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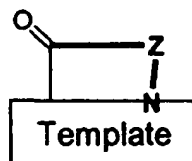
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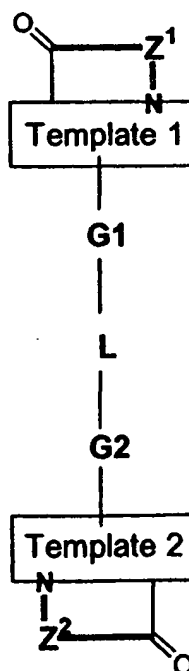
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(54) Title: TEMPLATE-FIXED PEPTIDOMIMETICS WITH ANTIMICROBIAL ACTIVITY



(Ia)



(Ib)

(57) Abstract: Template-fixed β -hairpin peptidomimetics of the general formulae (I) and (II) wherein Z, Z1 and Z2 are template-fixed chains of 8 to 16 α -amino acid residues which, depending on their positions in the chain (counted starting from the N-terminal amino acid) are Gly, or Pro, or of certain types which, as the remaining symbols in the above formulae, are defined in the description and the claims, and salts thereof, have the property to inhibit the growth of or to kill microorganisms and cancer cells. They can be used as disinfectants for foodstuffs, cosmetics, medicaments or other nutrient-containing materials or as medicaments to treat or prevent infections or diseases related to such infections and/or cancer. These β -hairpin peptidomimetics can be manufactured by a process which is based on a mixed solid- and solution phase synthetic strategy.

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TEMPLATE-FIXED PEPTIDOMIMETICS WITH ANTIMICROBIAL ACTIVITY

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The present invention provides template-fixed β -hairpin peptidomimetics incorporating template-fixed chains of 8 to 16 α -amino acid residues which, depending on their positions in the chains, are Gly or Pro, or of certain types, as defined hereinbelow. These template-fixed β -hairpin mimetics have broad spectrum antimicrobial and anticancer activity. In addition, the present invention provides an efficient synthetic process by which these compounds can, if desired, be made in parallel library-format. These β -hairpin peptidomimetics show improved efficacy, bioavailability, half-life and most importantly a significantly enhanced ratio between antibacterial and anticancer activity on the one hand, and hemolysis of red blood cells on the other.

15

The growing problem of microbial resistance to established antibiotics has stimulated intense interest in developing novel antimicrobial agents with new modes of action (H. Breithaupt, *Nat. Biotechnol.* 1999, 17, 1165-1169). One emerging class of antibiotics is based on naturally occurring cationic peptides (T. Ganz, R. I. Lehrer, *Mol. Medicine Today* 1999, 5, 292-297; R. M. Epand, H. J. Vogel, *Biochim. Biophys. Acta* 1999, 1462, 11-28). These include disulfide-bridged β -hairpin and β -sheet peptides (such as the *protegrins* [V. N. M.; O. V. Shamova, H. A. Korneva, R. I. Lehrer, *FEBS Lett.* 1993, 327, 231-236], *tachyplesins* [T. Nakamura, H. Furunaka, T. Miyata, F. Tokunaga, T. Muta, S. Iwanaga, M. Niwa, T. Takao, Y. Shimonishi, *Y. J. Biol. Chem.* 1988, 263, 16709-16713], and the *defensins* [R. I. Lehrer, A. K. Lichtenstein, T. Ganz, *Annu. Rev. Immunol.* 1993, 11, 105-128], amphipathic α -helical peptides (e.g. *cecropins*, *dermaseptins*, *magainins*, and *mellitins* [A. Tossi, L. Sandri, A. Giangaspero, *Biopolymers* 2000, 55, 4-30]), as well as other linear and loop-structured peptides. Although the mechanisms of action of antimicrobial cationic peptides are not yet fully understood, their primary site of interaction is the microbial cell membrane (H. W. Huang, *Biochemistry* 2000, 39, 8347-8352). Upon exposure to these agents, the cell membrane undergoes permeabilization, which is followed by rapid cell death. However, more complex mechanisms of action, for example, involving receptor-mediated signaling, cannot presently be ruled out (M. Wu, E. Maier, R. Benz, R. E. Hancock, *Biochemistry* 1999, 38, 7235-7242).

35

- The antimicrobial activities of many of these cationic peptides usually correlate with their preferred secondary structures, observed either in aqueous solution or in membrane-like environments (N. Sitaram, R. Nagaraj, *Biochim. Biophys. Acta* 1999, 1462, 29-54). Structural studies by nuclear magnetic resonance (NMR) spectroscopy have shown that cationic peptides such as protegrin 1 (A. Aumelas, M. Mangoni, C. Roumestand, L. Chiche, E. Despau, G. Grassy, B. Calas, A. Chavanieu, *Eur. J. Biochem.* 1996, 237, 575-583; R. L. Fahrner, T. Dieckmann, S. S. L. Harwig, R. I. Lehrer, D. Eisenberg, J. Feigon, *J. Chem. Biol.* 1996, 3, 543-550) and tachyplesin I (K. Kawano, T. Yoneya, T. Miyata, K. Yoshikawa, F. Tokunaga, Y. Terada, S. J. Iwanaga, *S. J. Biol. Chem.* 1990, 265, 15365-15367) adopt well defined β -hairpin conformations, due to the constraining effect of two disulfide bridges. In protegrin analogues lacking one or both of these disulfide bonds, the stability of the β -hairpin conformation is diminished, and the antimicrobial activity is reduced (J. Chen, T. J. Falla, H. J. Liu, M. A. Hurst, C. A. Fujii, D. A. Mosca, J. R. Embree, D. J. Lory, P. A. Radel, C. C. Chang, L. Gu, J. C. Fiddes, *Biopolymers* 2000, 55, 88-98; S. L. Harwig, A. Waring, H. J. Yang, Y. Cho, L. Tan, R. I. Lehrer, *R. J. Eur. J. Biochem.* 1996, 240, 352-357; M. E. Mangoni, A. Aumelas, P. Charnet, C. Roumestand, L. Chiche, E. Despau, G. Grassy, B. Calas, A. Chavanieu, *FEBS Lett.* 1996, 383, 93-98; H. Tamamura, T. Murakami, S. Noriuchi, K. Sugihara, A. Otake, W. Takada, T. Ibuka, M. Waki, N. Tamamoto, N. Fujii, *Chem. Pharm. Bull.* 1995, 43, 853-858). Similar observations have been made in analogues of tachyplesin I (H. Tamamura, R. Ikoma, M. Niwa, S. Funakoshi, T. Murakami, N. Fujii, *Chem. Pharm. Bull.* 1993, 41, 978-980) and in hairpin-loop mimetics of rabbit defensin NP-2 (S. Thennarasu, R. Nagaraj, *Biochem. Biophys. Res. Comm.* 1999, 254, 281-283). These results show that the β -hairpin structure plays an important role in the antimicrobial activity and stability of these protegrin-like peptides. In the case of the cationic peptides preferring α -helical structures, the amphiphilic structure of the helix appears to play a key role in determining antimicrobial activity (A. Tossi, L. Sandri, A. Giangaspero, *A. Biopolymers* 2000, 55, 4-30). Gramicidin S is a backbone-cyclic peptide with a well defined β -hairpin structure (S. E. Hull, R. Karlsson, P. Main, M. M. Woolfson, E. J. Dodson, *Nature* 1978, 275, 206-275) that displays potent antimicrobial activity against gram-positive and gram-negative bacteria (L. H. Kondejewski, S. W. Farmer, D. S. Wishart, R. E. Hancock, R. S. Hodges, *Int. J. Peptide Prot. Res.* 1996, 47, 460-466). The high hemolytic activity of gramicidin S has, however, hindered its widespread use as an antibiotic. Recent structural studies by NMR have indicated that the high hemolytic activity apparently correlates with the highly amphipathic nature of this cyclic β -hairpin-like molecule, but that it is possible to dissociate antimicrobial and hemolytic activities by modulating the conformation and amphiphilicity (L. H. Kondejewski, M. Jelokhani-Niaraki, S. W. Farmer, B. Lix, M. Kay, B. D. Sykes, R. E. Hancock, R. S. Hodges,

J. Biol. Chem. **1999**, *274*, 13181-13192; C. McInnes, L. H. Kondejewski, R. S. Hodges, B. D. Sykes, *J. Biol. Chem.* **2000**, *275*, 14287-14294).

A new cyclic antimicrobial peptide RTD-1 was reported recently from primate leukocytes
5 (Y.-Q. Tang, J. Yuan, G. Ösapay, K. Ösapay, D. Tran, C. J. Miller, A. J. Oellette, M. E. Selsted, *Science* **1999**, *286*, 498-502. This peptide contains three disulfide bridges, which act to constrain the cyclic peptide backbone into a hairpin geometry. Cleavage of the three disulfide bonds leads to a significant loss of antimicrobial activity. Analogues of protegrins (J. P. Tam, C. Wu, J.-L. Yang, *Eur. J. Biochem.* **2000**, *267*, 3289-3300) and tachyplesins (J.-P.
10 Tam, Y.-A. Lu, J.-L. Yang, *Biochemistry* **2000**, *39*, 7159-7169; N. Sitaram, R. Nagaraj, *Biochem. Biophys. Res. Comm.* **2000**, *267*, 783-790) containing a cyclic peptide backbone, as well as multiple disulfide bridges to enforce an amphiphilic hairpin structure, have also been reported. In these cases, removal of all the cystine constraints does not always lead to a large loss of antimicrobial activity, but does modulate the membranolytic selectivity (J. P. Tam, C.
15 Wu, J.-L. Yang, *Eur. J. Biochem.* **2000**, *267*, 3289-3300).

A key issue in the design of new cationic antimicrobial peptides is selectivity. The naturally occurring protegrins and tachyplesins exert a significant hemolytic activity against human red blood cells. This is also the case for protegrin analogues such as IB367 (J. Chen, T. J. Falla, H. J. Liu, M. A. Hurst, C. A. Fujii, D. A. Mosca, J. R. Embree, D. J. Loury, P. A. Radcl, C. C.
20 Chang, L. Gu, J. C. Fiddes, *Biopolymers* **2000**, *55*, 88-98; C. Chang, L. Gu, J. Chen, *US-Pat.* **5,916,872**, **1999**). This high hemolytic activity essentially obviates its use in vivo, and represents a serious disadvantage in clinical applications. Also, the antibiotic activity of analogues often decreases significantly with increasing salt concentration, such that under in vivo conditions (ca. 100-150 mM NaCl) the antimicrobial activity may be severely reduced.
25 Before intravenous use can be considered, the general toxicity, protein-binding activity in blood serum, as well as protease stability become serious issues which must be adequately addressed.

Protegrin 1 exhibits potent and similar activity against gram-positive and gram-negative
30 bacteria as well as fungi in both low- and high-salt assays. This broad antimicrobial activity combined with a rapid mode of action, and their ability to kill bacteria resistant to other classes of antibiotics, make them attractive targets for development of clinically useful antibiotics. The activity against gram-positive bacteria is typically higher than against gram-negative bacteria. However, protegrin 1 also exhibits a high hemolytic activity against human
35 red blood cells, and hence a low selectivity towards microbial cells. Oriented CD experiments (W. T. Heller, A. J. Waring, R. I. Lehrer, H. W. Huang, *Biochemistry* **1998**, *37*, 17331-17338) indicate that protegrin 1 may exist in two different states as it interacts with membranes, and

these states are strongly influenced by lipid composition. Studies of cyclic protegrin analogues (J.-P. Tam, C. Wu, J.-L. Yang, *Eur. J. Biochem.* **2000**, *267*, 3289-3300) have revealed, that an increase in the conformational rigidity, resulting from backbone cyclization and multiple disulfide bridges, may confer membranolytic selectivity that dissociates antimicrobial activity from hemolytic activity, at least in the series of compounds studied.

5 *Protegrin 1* is an 18 residues linear peptide, with an amidated carboxyl terminus and two disulfide bridges. *Tachyplesin 1* contains 17 residues, also has an amidated carboxyl terminus and contains two disulfide bridges. Recently described backbone-cyclic protegrin and tachyplesin analogues typically contain 18 residues and up to three disulfide bridges (J. P.

10 Tam, C. Wu, J.-L. Yang, *Eur. J. Biochem.* **2000**, *267*, 3289-3300; J. P. Tam, Y.-A. Lu, J.-L. Yang, *Biochemistry* **2000**, *39*, 7159-7169; N. Sitaram, R. Nagaraj, *Biochem. Biophys. Res. Comm.* **2000**, *267*, 783-790).

Cathelicidin, a 37-residue linear helical-type cationic peptide, and analogues are currently under investigation as inhaled therapeutic agents for *cystic fibrosis*(CF) lung disease (L.

15 Saiman, S. Tabibi, T. D. Starner, P. San Gabriel, P. L. Winokur, H. P. Jia, P. B. McGray, Jr., B. F. Tack, *Antimicrob. Agents and Chemother.* **2001**, *45*, 2838-2844; R. E. W. Hancock, R. Lehrer, *Trends Biotechnol.* **1998**, *16*, 82-88). Over 80% of CF patients become chronically infected with *pseudomonas aeruginosa* (C. A. Demko, P. J. Biard, P. B. Davies, *J. Clin. Epidemiol.* **1995**, *48*, 1041-1049; E. M. Kerem, R. Gold, H. Levinson, *J. Pediatr.* **1990**, *116*,

20 714-719).

In addition, there is evidence from the literature that some cationic peptides exhibit interesting anticancer activity. *Cerecropin B*, a 35-residue α -helical cationic peptide isolated from the hemolymph of the giant silk moth, and shorter analogues derived from *Cerecropin B* have been investigated as potential anticancer compounds (A. J. Moore, D. A. Devine, M. C.

25 Bibby, *Peptide Research* **1994**, *7*, 265-269).

In the compounds described below, a new strategy is introduced to stabilize β -hairpin conformations in backbone-cyclic cationic peptide mimetic exhibiting antimicrobial and anticancer activity. This involves transplanting the cationic and hydrophobic hairpin sequence onto a template, whose function is to restrain the peptide loop backbone into a hairpin

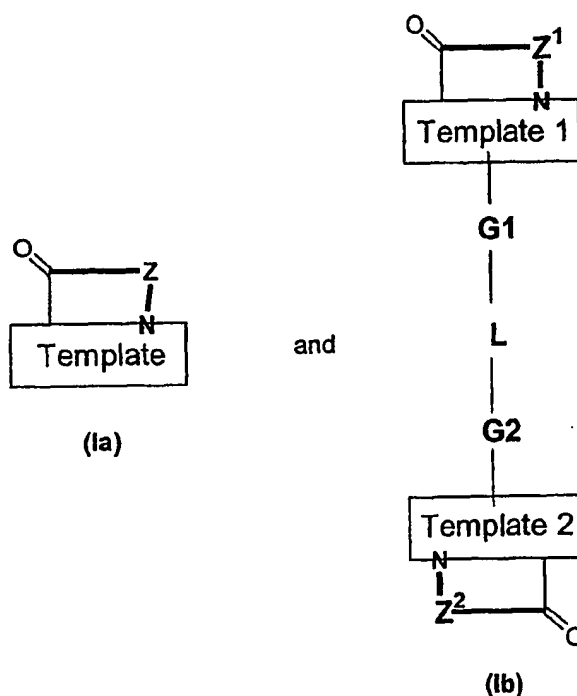
30 geometry. The rigidity of the hairpin may be further influenced by introducing a disulfide bridge. The template moiety may also act as an attachment point for other organic groups, that may modulate the antimicrobial and/or membranolytic targeting selectivity of the molecule, and be useful for producing dimeric species, where the templates in each monomer unit are linked through a short spacer or linker. Template-bound hairpin mimetic peptides have been

35 described in the literature (D. Obrecht, M. Altorfer, J. A. Robinson, *Adv. Med. Chem.* **1999**, *4*, 1-68; J. A. Robinson, *Syn. Lett.* **2000**, *4*, 429-441), but such molecules have not previously

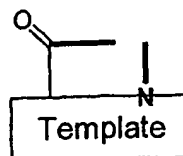
been evaluated for development of antimicrobial peptides. However, the ability to generate β -hairpin peptidomimetics using combinatorial and parallel synthesis methods has now been established (L. Jiang, K. Moehle, B. Dhanapal, D. Obrecht, J. A. Robinson, *Helv. Chim. Acta.* 2000, 83, 3097-3112).

- 5 These methods allow the synthesis and screening of large hairpin mimetic libraries, which in turn considerably facilitates structure-activity studies, and hence the discovery of new molecules with potent antimicrobial and anticancer activity and low hemolytic activity to human red blood cells. Furthermore, the present strategy allows to synthesize β -hairpin peptidomimetics with novel selectivities towards different types of pathogens, e.g. towards
- 10 various multi-drug resistant *pseudomonas* strains. β -Hairpin peptidomimetics obtained by the approach described here can be used amongst other applications, e.g. as broad spectrum antibiotics, as therapeutics for *cystic fibrosis* lung disease and anticancer agents.

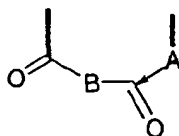
- The β -hairpin peptidomimetics of the present invention are compounds of the general
- 15 formulae



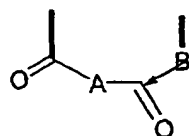
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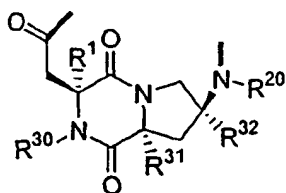


(a1)

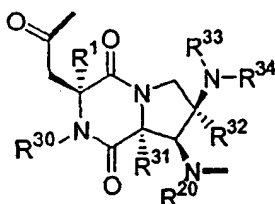


(a2)

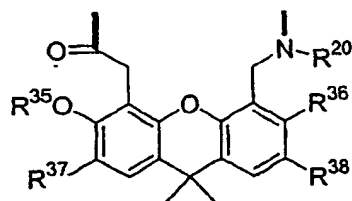
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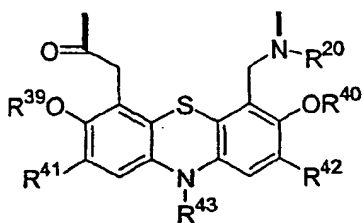
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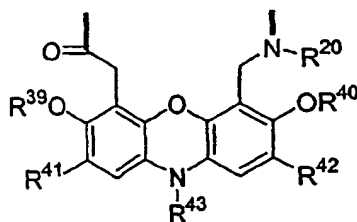
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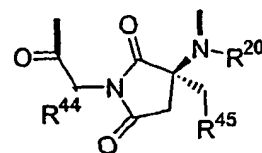
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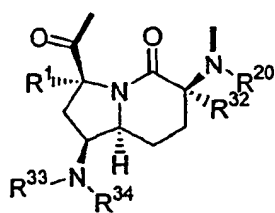
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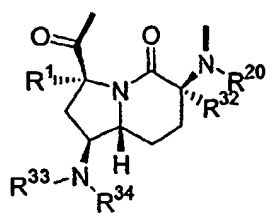
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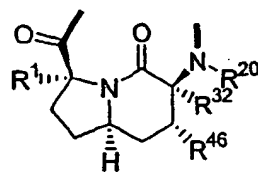
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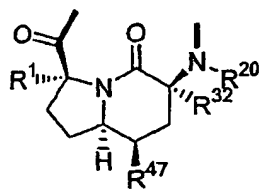
(e1)



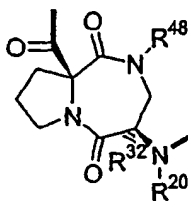
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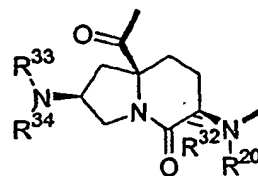
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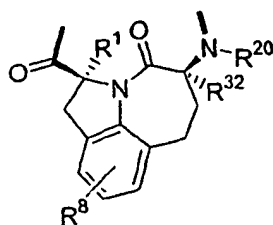
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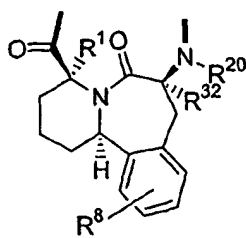
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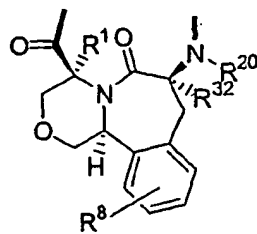
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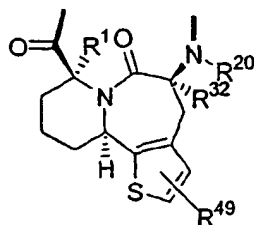
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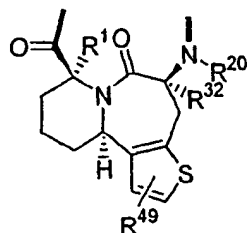
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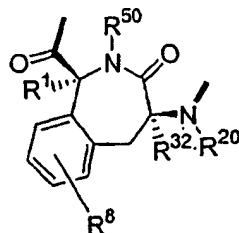
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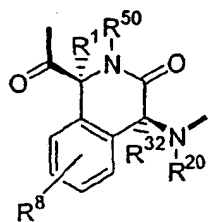
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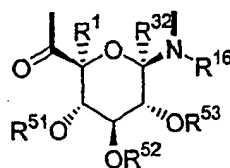
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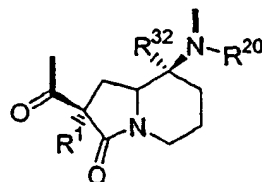
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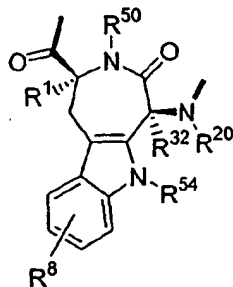
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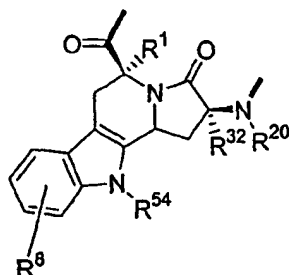
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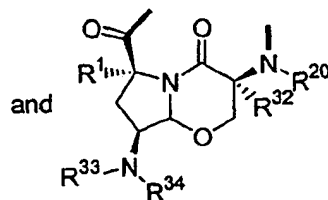
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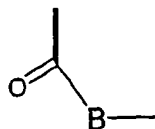


(o)



(p)

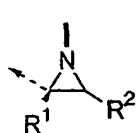
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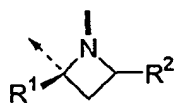
is the residue of an L- α -amino acid with B being a residue of formula $-NR^{20}CH(R^{71})-$ or the enantiomer of one of the groups A1 to A69 as defined hereinafter;



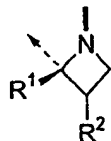
is a group of one of the formulae



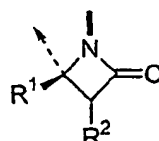
A1



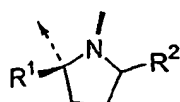
A2



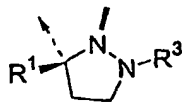
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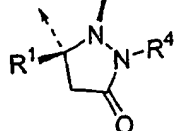
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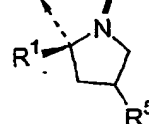
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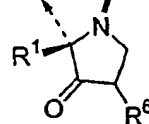
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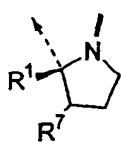
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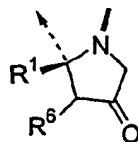
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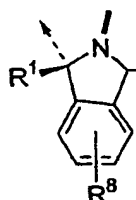
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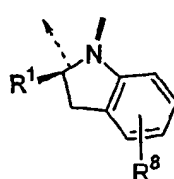
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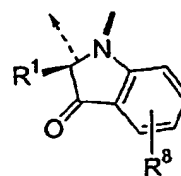
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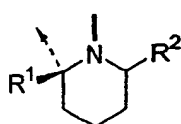
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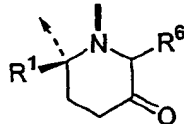
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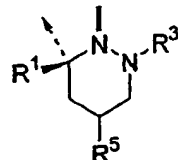
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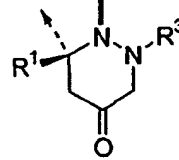
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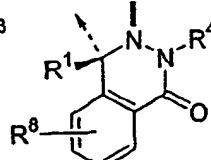
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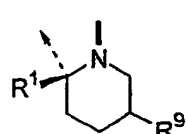
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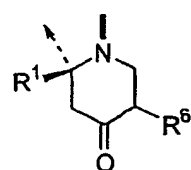
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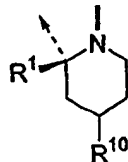
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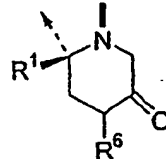
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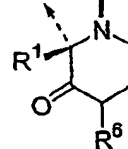
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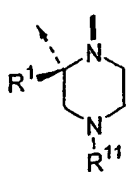
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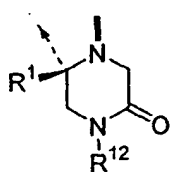
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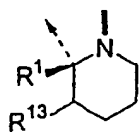
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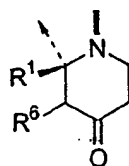
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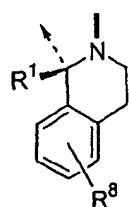
A26



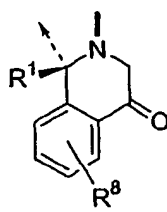
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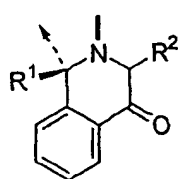
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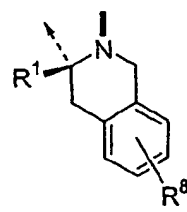
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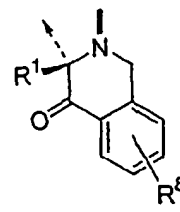
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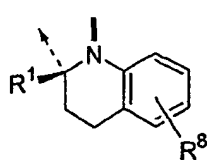
A31



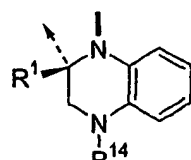
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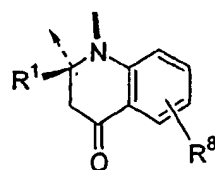
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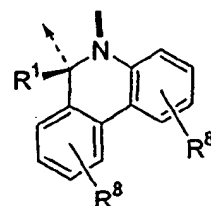
A34



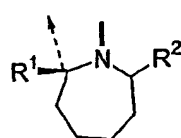
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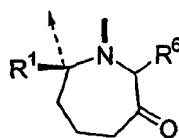
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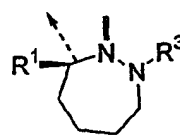
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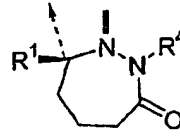
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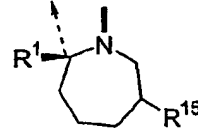
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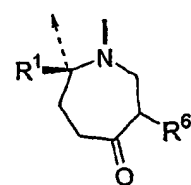
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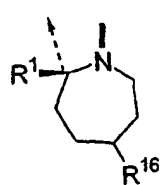
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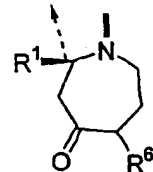
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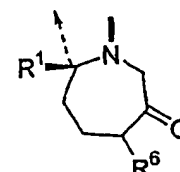
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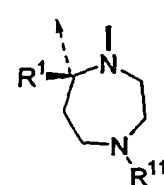
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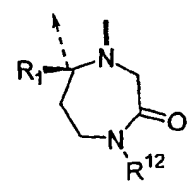
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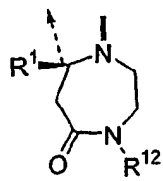
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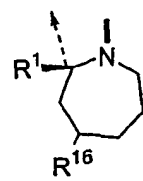
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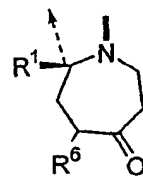
A48



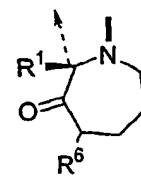
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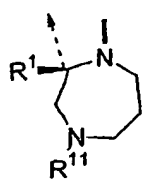
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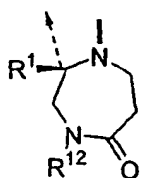
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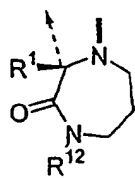
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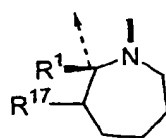
A53



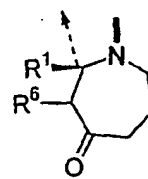
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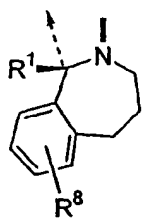
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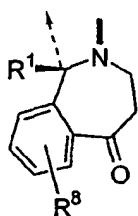
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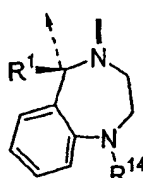
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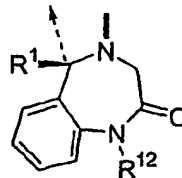
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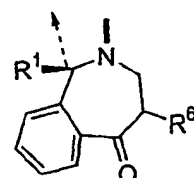
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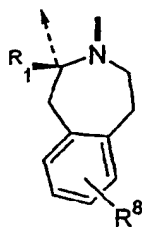
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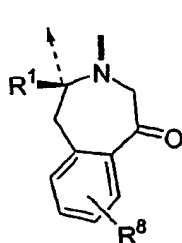
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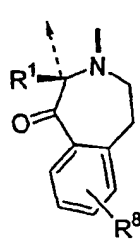
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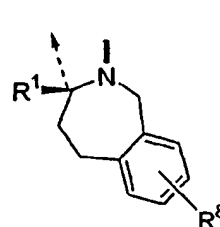
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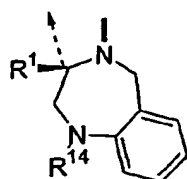
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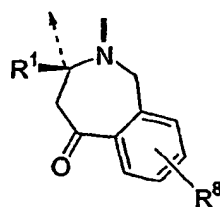
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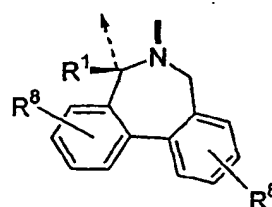
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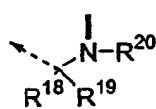
A67



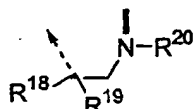
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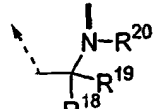
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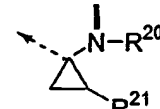
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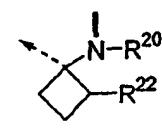
A71



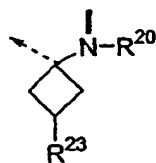
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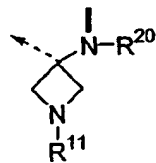
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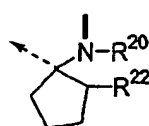
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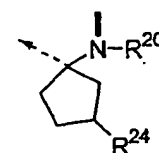
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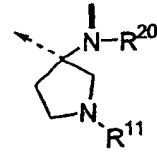
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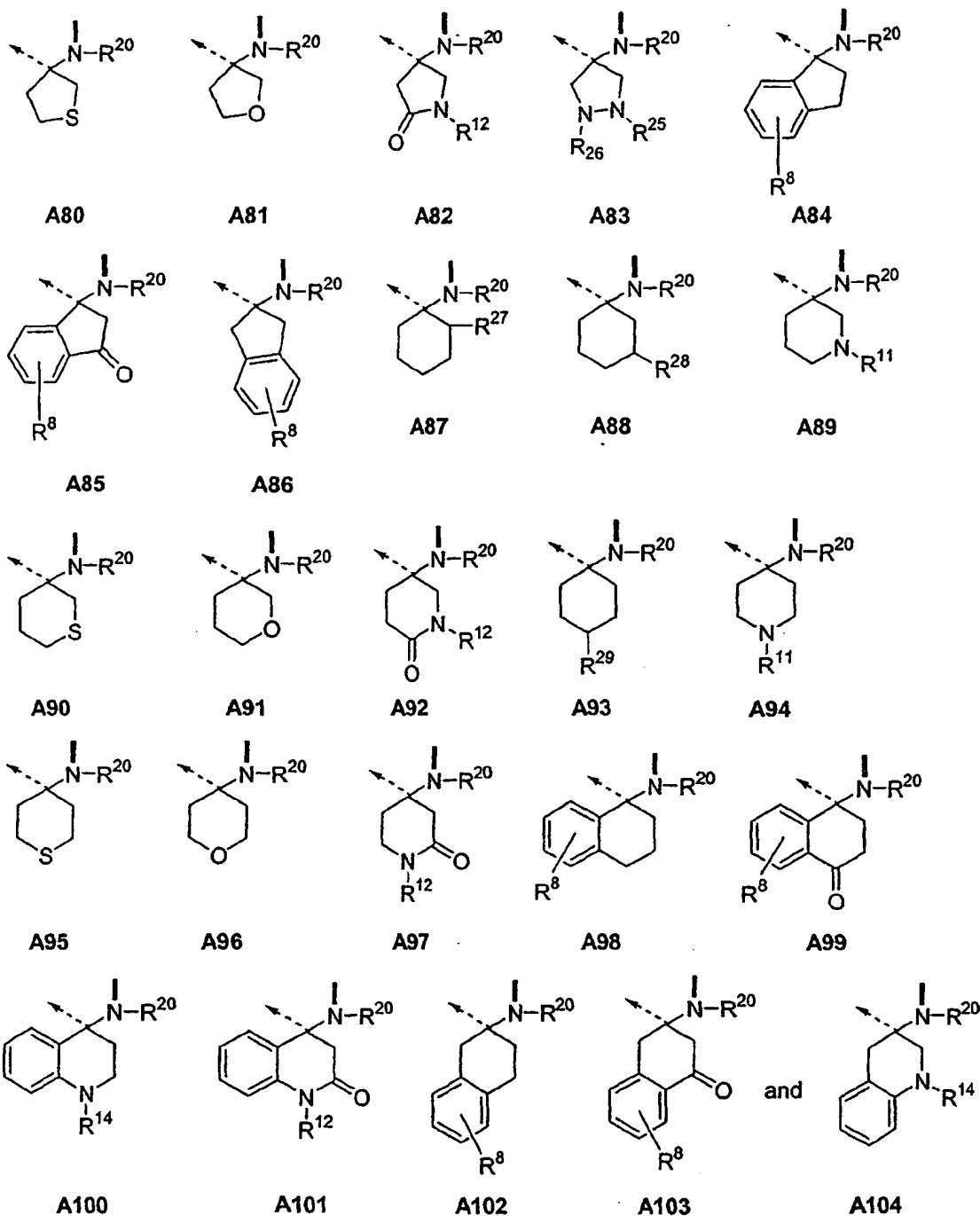
A77



A78



A79



R^1 is H; lower alkyl; or aryl-lower alkyl;

R^2 is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sSR^{56}$;
 $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$;
 $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sCOOR^{57}$;
 $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^3 is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sSR^{56}$;

- $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$;
 $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sCOOR^{57}$;
 $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
5 R^4 is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sSR^{56}$;
 $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_p(CHR^{61})_sCOOR^{57}$; $-(CH_2)_p(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_p(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_p(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
10 R^5 is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R^6 is H; alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$;
15 $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R^7 is alkyl; alkenyl; $-(CH_2)_q(CHR^{61})_sOR^{55}$; $-(CH_2)_q(CHR^{61})_sNR^{33}R^{34}$;
20 $-(CH_2)_q(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_q(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_r(CHR^{61})_sCOOR^{57}$; $-(CH_2)_r(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_r(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_r(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_r(CHR^{61})_sC_6H_4R^8$;
 R^8 is H; Cl; F; CF₃; NO₂; lower alkyl; lower alkenyl; aryl; aryl-lower alkyl;
 $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
25 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sCOR^{64}$;
 R^9 is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
30 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R^{10} is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$;
 $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
35 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R^{11} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$;

- $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R¹² is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sSR^{56}$;
 5 $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$;
 $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_m(CHR^{61})_sCOOR^{57}$;
 $-(CH_2)_m(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_m(CHR^{61})_sPO(OR^{60})_2$; $-(CH_2)_m(CHR^{61})_sSO_2R^{62}$; or
 $-(CH_2)_m(CHR^{61})_sC_6H_4R^8$;
 R¹³ is alkyl; alkenyl; $-(CH_2)_q(CHR^{61})_sOR^{55}$; $-(CH_2)_q(CHR^{61})_sSR^{56}$; $-(CH_2)_q(CHR^{61})_sNR^{33}R^{34}$;
 10 $-(CH_2)_q(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_q(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_q(CHR^{61})_sCOOR^{57}$; $-(CH_2)_q(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_q(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_q(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_q(CHR^{61})_sC_6H_4R^8$;
 R¹⁴ is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 15 $-(CH_2)_q(CHR^{61})_sCOOR^{57}$; $-(CH_2)_q(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_q(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_q(CHR^{61})_sSOR^{62}$; or $-(CH_2)_q(CHR^{61})_sC_6H_4R^8$;
 R¹⁵ is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 20 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R¹⁶ is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 25 R¹⁷ is alkyl; alkenyl; $-(CH_2)_q(CHR^{61})_sOR^{55}$; $-(CH_2)_q(CHR^{61})_sSR^{56}$; $-(CH_2)_q(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_q(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_q(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_q(CHR^{61})_sCOOR^{57}$; $-(CH_2)_q(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_q(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_q(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_q(CHR^{61})_sC_6H_4R^8$;
 R¹⁸ is alkyl; alkenyl; $-(CH_2)_p(CHR^{61})_sOR^{55}$; $-(CH_2)_p(CHR^{61})_sSR^{56}$; $-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$;
 30 $-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_p(CHR^{61})_sCOOR^{57}$; $-(CH_2)_p(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_p(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_p(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_p(CHR^{61})_sC_6H_4R^8$;
 R¹⁹ is lower alkyl; $-(CH_2)_p(CHR^{61})_sOR^{55}$; $-(CH_2)_p(CHR^{61})_sSR^{56}$; $-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 35 $-(CH_2)_p(CHR^{61})_sCOOR^{57}$; $-(CH_2)_p(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_p(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_p(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_p(CHR^{61})_sC_6H_4R^8$; or
 R¹⁸ and R¹⁹ taken together can form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or

- $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R^{28} is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
5 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R^{29} is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
10 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R^{30} is H; alkyl; alkenyl; or aryl-lower alkyl;
 R^{31} is H; alkyl; alkenyl; $-(CH_2)_p(CHR^{61})_sOR^{55}$; $-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
15 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R^{32} is H; lower alkyl; or aryl-lower alkyl;
 R^{33} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sNR^{34}R^{63}$;
 $-(CH_2)_m(CHR^{61})_sOCONR^{75}R^{82}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{78}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOR^{64}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
20 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R^{34} is H; lower alkyl; aryl, or aryl-lower alkyl;
 R^{33} and R^{34} taken together can form: $-(CH_2)_2$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or
 $-(CH_2)_2NR^{57}(CH_2)_2$;
 R^{35} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$;
25 $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_p(CHR^{61})_sCOOR^{57}$; $-(CH_2)_p(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_p(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_p(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_p(CHR^{61})_sC_6H_4R^8$;
 R^{36} is H; alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
30 $-(CH_2)_p(CHR^{61})_sCOOR^{57}$; $-(CH_2)_p(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_p(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_p(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R^{37} is H; F; Br; Cl; NO_2 ; CF_3 ; lower alkyl; $-(CH_2)_p(CHR^{61})_sOR^{55}$; $-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
35 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R^{38} is H; F; Br; Cl; NO_2 ; CF_3 ; alkyl; alkenyl; $-(CH_2)_p(CHR^{61})_sOR^{55}$;
 $-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$;

$-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^{39} is H; alkyl; alkenyl; or aryl-lower alkyl;

5 R^{40} is H; alkyl; alkenyl; or aryl-lower alkyl;

R^{41} is H; F; Br; Cl; NO_2 ; CF_3 ; alkyl; alkenyl; $-(CH_2)_p(CHR^{61})_sOR^{55}$;

$-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$;

$-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;

$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;

10 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^{42} is H; F; Br; Cl; NO_2 ; CF_3 ; alkyl; alkenyl; $-(CH_2)_p(CHR^{61})_sOR^{55}$;

$-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$;

$-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;

$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;

15 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^{43} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$;

$-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;

$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;

$-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

20 R^{44} is alkyl; alkenyl; $-(CH_2)_r(CHR^{61})_sOR^{55}$; $-(CH_2)_r(CHR^{61})_sSR^{56}$; $-(CH_2)_r(CHR^{61})_sNR^{33}R^{34}$;

$-(CH_2)_r(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_r(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;

$-(CH_2)_r(CHR^{61})_sCOOR^{57}$; $-(CH_2)_r(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_r(CHR^{61})_sPO(OR^{60})_2$;

$-(CH_2)_r(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_r(CHR^{61})_sC_6H_4R^8$;

R^{45} is H; alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$; -

25 $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;

$-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;

$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;

$-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^{46} is H; alkyl; alkenyl; or $-(CH_2)_o(CHR^{61})_pC_6H_4R^8$;

30 R^{47} is H; alkyl; alkenyl; or $-(CH_2)_o(CHR^{61})_sOR^{55}$;

R^{48} is H; lower alkyl; lower alkenyl; or aryl-lower alkyl;

R^{49} is H; alkyl; alkenyl; $-(CHR^{61})_sCOOR^{57}$; $(CHR^{61})_sCONR^{58}R^{59}$; $(CHR^{61})_sPO(OR^{60})_2$;

$-(CHR^{61})_sSOR^{62}$; or $-(CHR^{61})_sC_6H_4R^8$;

R^{50} is H; lower alkyl; or aryl-lower alkyl;

35 R^{51} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sSR^{56}$;

$-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$;

$-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sCOOR^{57}$;

- $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_pPO(OR^{60})_2$;
 $-(CH_2)_p(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_p(CHR^{61})_sC_6H_4R^8$;
 R^{52} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sSR^{56}$;
 $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$;
5 $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sCOOR^{57}$;
 $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_pPO(OR^{60})_2$;
 $-(CH_2)_p(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_p(CHR^{61})_sC_6H_4R^8$;
 R^{53} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sSR^{56}$;
 $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$;
10 $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sCOOR^{57}$;
 $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_pPO(OR^{60})_2$;
 $-(CH_2)_p(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_p(CHR^{61})_sC_6H_4R^8$;
 R^{54} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
15 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R^{55} is H; lower alkyl; lower alkenyl; aryl-lower alkyl; $-(CH_2)_m(CHR^{61})_sOR^{57}$;
 $-(CH_2)_m(CHR^{61})_sNR^{34}R^{63}$; $-(CH_2)_m(CHR^{61})_sOCONR^{75}R^{82}$;
 $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{78}R^{82}$; $-(CH_2)_o(CHR^{61})_s-COR^{64}$; $-(CH_2)_o(CHR^{61})_sCOOR^{57}$;
or
20 $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
 R^{56} is H; lower alkyl; lower alkenyl; aryl-lower alkyl; $-(CH_2)_m(CHR^{61})_sOR^{57}$;
 $-(CH_2)_m(CHR^{61})_sNR^{34}R^{63}$; $-(CH_2)_m(CHR^{61})_sOCONR^{75}R^{82}$;
 $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{78}R^{82}$; $-(CH_2)_o(CHR^{61})_s-COR^{64}$; or
 $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
25 R^{57} is H; lower alkyl; lower alkenyl; aryl lower alkyl; or heteroaryl lower alkyl;
 R^{58} is H; lower alkyl; lower alkenyl; aryl; heteroaryl; aryl-lower alkyl; or heteroaryl-lower
alkyl;
 R^{59} is H; lower alkyl; lower alkenyl; aryl; heteroaryl; aryl-lower alkyl; or heteroaryl-lower
alkyl; or
30 R^{58} and R^{59} taken together can form: $-(CH_2)_2-6-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or
 $-(CH_2)_2NR^{57}(CH_2)_2-$;
 R^{60} is H; lower alkyl; lower alkenyl; aryl; or aryl-lower alkyl;
 R^{61} is alkyl; alkenyl; aryl; heteroaryl; aryl-lower alkyl; heteroaryl-lower alkyl; $-(CH_2)_mOR^{55}$;
 $-(CH_2)_mNR^{33}R^{34}$; $-(CH_2)_mOCONR^{75}R^{82}$; $-(CH_2)_mNR^{20}CONR^{78}R^{82}$; $-(CH_2)_oCOOR^{37}$;
35 $-(CH_2)_oNR^{58}R^{59}$; or $-(CH_2)_oPO(COR^{60})_2$;
 R^{62} is lower alkyl; lower alkenyl; aryl, heteroaryl; or aryl-lower alkyl;

R^{63} is H; lower alkyl; lower alkenyl; aryl, heteroaryl; aryl-lower alkyl; heteroaryl-lower alkyl;

$-\text{COR}^{64}$; $-\text{COOR}^{57}$; $-\text{CONR}^{58}\text{R}^{59}$; $-\text{SO}_2\text{R}^{62}$; or $-\text{PO}(\text{OR}^{60})_2$;

R^{34} and R^{63} taken together can form: $-(\text{CH}_2)_2\text{-}$; $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{-}$; $-(\text{CH}_2)_2\text{S}(\text{CH}_2)_2\text{-}$; or

5 $-(\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_2\text{-}$;

R^{64} is H; lower alkyl; lower alkenyl; aryl; heteroaryl; aryl-lower alkyl; heteroaryl-lower alkyl;

$-(\text{CH}_2)_p(\text{CHR}^{61})_s\text{OR}^{65}$; $-(\text{CH}_2)_p(\text{CHR}^{61})_s\text{SR}^{66}$; or $-(\text{CH}_2)_p(\text{CHR}^{61})_s\text{NR}^{34}\text{R}^{63}$;

$-(\text{CH}_2)_p(\text{CHR}^{61})_s\text{OCONR}^{75}\text{R}^{82}$; $-(\text{CH}_2)_p(\text{CHR}^{61})_s\text{NR}^{20}\text{CONR}^{78}\text{R}^{82}$;

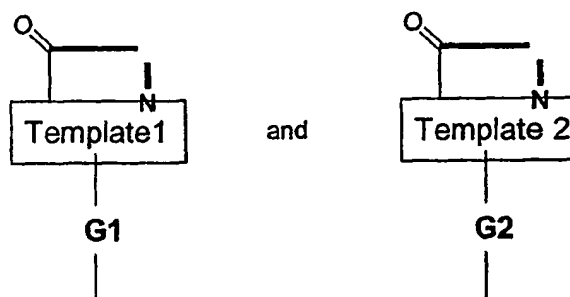
R^{65} is H; lower alkyl; lower alkenyl; aryl, aryl-lower alkyl; heteroaryl-lower alkyl; $-\text{COR}^{57}$;

10 $-\text{COOR}^{57}$; or $-\text{CONR}^{58}\text{R}^{59}$;

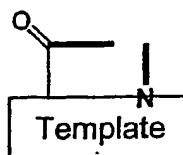
R^{66} is H; lower alkyl; lower alkenyl; aryl; aryl-lower alkyl; heteroaryl-lower alkyl; or

$-\text{CONR}^{58}\text{R}^{59}$;

m is 2-4; o is 0-4; p is 1-4; q is 0-2; r is 1 or 2; s is 0 or 1;



15 independently have any of the significances defined above for



except (a1) or (a2) with B being $-\text{NR}^{20}\text{CH}(\text{R}^{71})\text{-}$ and with A being A80, A81, A90, A91, A95 or A96, and except (f) and (m), but wherein

20 R^2 is $-(\text{CH}_2)_m(\text{CHR}^{61})_s\text{O-}$; $-(\text{CH}_2)_m(\text{CHR}^{61})_s\text{S-}$; $-(\text{CH}_2)_m(\text{CHR}^{61})_s\text{NR}^{34}\text{-}$; or $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{CO-}$;

R^3 is $-(\text{CH}_2)_m(\text{CHR}^{61})_s\text{O-}$; $-(\text{CH}_2)_m(\text{CHR}^{61})_s\text{S-}$; $-(\text{CH}_2)_m(\text{CHR}^{61})_s\text{NR}^{34}\text{-}$; or $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{CO-}$;

R^4 is $-(\text{CH}_2)_m(\text{CHR}^{61})_s\text{O-}$; $-(\text{CH}_2)_m(\text{CHR}^{61})_s\text{S-}$; $-(\text{CH}_2)_m(\text{CHR}^{61})_s\text{NR}^{34}\text{-}$; or

25 $-(\text{CH}_2)_p(\text{CHR}^{61})_s\text{CO-}$;

R^5 is $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{O-}$; $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{S-}$; $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{NR}^{34}\text{-}$; or

- $-(CH_2)_o(CHR^{61})_sCO-$;
 R^6 is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or
 $-(CH_2)_o(CHR^{61})_sCO-$;
 R^7 is $-(CH_2)_q(CHR^{61})_sO-$; $-(CH_2)_q(CHR^{61})_sNR^{34}-$; or $-(CH_2)_r(CHR^{61})_sCO-$;
5 R^8 is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or
 $-(CH_2)_o(CHR^{61})_sCO-$;
 R^9 is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or
 $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{10} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or
10 $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{11} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{12} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_r(CHR^{61})_sCO-$;
 R^{13} is $-(CH_2)_q(CHR^{61})_sO-$; $-(CH_2)_q(CHR^{61})_sS-$; $-(CH_2)_q(CHR^{61})_sNR^{34}-$; or
 $-(CH_2)_q(CHR^{61})_sCO-$;
15 R^{14} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_q(CHR^{61})_sCO-$;
 R^{15} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or
 $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{16} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or
 $-(CH_2)_o(CHR^{61})_sCO-$;
20 R^{17} is $-(CH_2)_q(CHR^{61})_sO-$; $-(CH_2)_q(CHR^{61})_sS-$; $-(CH_2)_q(CHR^{61})_sNR^{34}-$; or
 $-(CH_2)_q(CHR^{61})_sCO-$;
 R^{18} is $-(CH_2)_p(CHR^{61})_sO-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sNR^{34}-$; or
 $-(CH_2)_p(CHR^{61})_sCO-$;
 R^{19} is $-(CH_2)_p(CHR^{61})_sO-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sNR^{34}-$; or
25 $-(CH_2)_p(CHR^{61})_sCO-$;
 R^{21} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or
 $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{22} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or
 $-(CH_2)_o(CHR^{61})_sCO-$;
30 R^{23} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or
 $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{24} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or
 $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{25} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or
35 $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{26} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or
 $-(CH_2)_o(CHR^{61})_sCO-$;

- R^{27} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or
 $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{28} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or
 $-(CH_2)_o(CHR^{61})_sCO-$;
5 R^{29} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or
 $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{31} is $-(CH_2)_p(CHR^{61})_sO-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sNR^{34}-$; or
 $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{33} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;
10 R^{37} is $-(CH_2)_p(CHR^{61})_sO-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sNR^{34}-$; or
 $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{38} is $-(CH_2)_p(CHR^{61})_sO-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sNR^{34}-$; or
 $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{41} is $-(CH_2)_p(CHR^{61})_sO-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sNR^{34}-$; or
15 $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{42} is $-(CH_2)_p(CHR^{61})_sO-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sNR^{34}-$; or
 $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{43} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{45} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or
20 $-(CH_2)_s(CHR^{61})_sCO-$;
 R^{47} is $-(CH_2)_o(CHR^{61})_sO-$;
 R^{49} is $-(CHR^{61})_sO-$; $-(CHR^{61})_sS-$; $-(CHR^{61})_sNR^{34}-$; or $-(CHR^{61})_sCO-$;
 R^{51} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or
 $-(CH_2)_o(CHR^{61})_sCO-$;
25 R^{52} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or
 $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{53} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or
 $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{54} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;
30 R^{55} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{56} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{64} is $-(CH_2)_p(CHR^{61})_sO-$; $-(CH_2)_p(CHR^{61})_sS-$; or $-(CH_2)_p(CHR^{61})_sNR^{34}-$;

m, o, p, q, r and s being as defined above;

- with the proviso that if more than one of the substituents R^2 to R^{19} , R^{21} to R^{29} , R^{31} , R^{33} , R^{37} ,
 35 R^{38} , R^{41} to R^{43} , R^{45} , R^{47} , R^{49} , R^{51} to R^{56} and R^{64} is present, only one of these has one of the
 significances just mentioned whilst the other(s) has/have any of the significance(s) mentioned
 earlier;

L is a direct bond or one of the linkers

- L1: $-(CH_2)_pCHR^{61}[X(CH_2)_pCHR^{61}]_o-$;
 L2: $-CO(CH_2)_pCHR^{61}[X(CH_2)_pCHR^{61}]_oCO-$;
 5 L3: $-CONR^{34}(CH_2)_pCHR^{61}[X(CH_2)_pCHR^{61}]_oNR^{34}CO-$;
 L4: $-O(CH_2)_pCHR^{61}[X(CH_2)_pCHR^{61}]_oO-$;
 L5: $-S(CH_2)_pCHR^{61}[X(CH_2)_pCHR^{61}]_oS-$;
 L6: $-NR^{34}(CH_2)_pCHR^{61}[X(CH_2)_pCHR^{61}]_oNR^{34}-$;
 L7: $-(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}-$;
 10 L8: $-CO(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}CO-$;
 L9: $-CONR^{34}(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}NR^{34}CO-$;
 L10: $-O(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}O-$;
 L11: $-S(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}S-$;
 L12: $-NR^{34}(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}NR^{34}-$;
 15 L13: $-CO(CH_2)_pCHR^{61}[X(CH_2)_pCHR^{61}]_oNR^{34}-$;
 L14: $-CO(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}NR^{34}-$;
 L15: $-NR^{34}(CH_2)_pCHR^{61}[X(CH_2)_pCHR^{61}]_oCO-$; and
 L16: $-NR^{34}(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}CO-$;
 m, o, p, q, r and s being as defined above; X being O; S; NR^{34} ; $-NR^{32}CONR^{34}-$; or $-OCOO-$;
 20 and Y being $-C_6R^{67}R^{68}R^{69}R^{70}-$;
 R^{67} being H; Cl; Br; F; NO_2 ; $-NR^{34}COR^{57}$; lower alkyl; or lower alkenyl;
 R^{68} being H; Cl; Br; F; NO_2 ; $-NR^{34}COR^{57}$; lower alkyl; or lower alkenyl;
 R^{69} being H; Cl; Br; F; NO_2 ; $-NR^{34}COR^{57}$; lower alkyl; or lower alkenyl; and
 R^{70} being H; Cl; Br; F; NO_2 ; $-NR^{34}COR^{57}$; lower alkyl; or lower alkenyl;
 25 with the proviso that at least two of R^{67} , R^{68} , R^{69} and R^{70} are H; and

with the further proviso that

- $-(CH_2)_m(CHR^{61})_sO-$ can be combined with linker L1, L2, L3, L7, L8 or L9;
 $-(CH_2)_o(CHR^{61})_sO-$ can be combined with linker L1, L2, L3, L7, L8 or L9;
 30 $-(CH_2)_p(CHR^{61})_sO-$ can be combined with linker L1, L2, L3, L7, L8 or L9;
 $-(CH_2)_q(CHR^{61})_sO-$ can be combined with linker L1, L2, L3, L7, L8 or L9;
 $-(CHR^{61})_sO-$ can be combined with linker L1, L2, L3, L7, L8 or L9;
 $-(CH_2)_m(CHR^{61})_sS-$ can be combined with linker L1, L2, L3, L7, L8 or L9; or can form a
 disulfide bond with $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sS-$;
 35 $-(CH_2)_q(CHR^{61})_sS-$; or $-(CHR^{61})_sS-$;

- $-(CH_2)_o(CHR^{61})_sS-$ can be combined with linker L1, L2, L3, L7, L8 or L9; or can form a disulfide bond with $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_q(CHR^{61})_sS-$; or $-(CHR^{61})_sS-$;
- 5 $-(CH_2)_p(CHR^{61})_sS-$ can be combined with linker L1, L2, L3, L7, L8 or L9; or can form a disulfide bond with $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_q(CHR^{61})_sS-$; or $-(CHR^{61})_sS-$;
- $-(CH_2)_q(CHR^{61})_sS-$ can be combined with linker L1, L2, L3, L7, L8 or L9; or can form a disulfide bond with $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_q(CHR^{61})_sS-$; or $-(CHR^{61})_sS-$;
- 10 $-(CHR^{61})_sS-$ can be combined with linker L1, L2, L3, L7, L8 or L9; or form a disulfide bond with $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_q(CHR^{61})_sS-$; or $-(CHR^{61})_sS-$;
- $-(CH_2)_m(CHR^{61})_sNR^{34}-$ can be combined with linker L1, L2, L3, L7, L8 or L9;
- 15 $-(CH_2)_o(CHR^{61})_sNR^{34}-$ can be combined with linker L1, L2, L3, L7, L8 or L9;
- $-(CH_2)_p(CHR^{61})_sNR^{34}-$ can be combined with linker L1, L2, L3, L7, L8 or L9;
- $-(CH_2)_q(CHR^{61})_sNR^{34}-$ can be combined with linker L1, L2, L3, L7, L8 or L9;
- $-(CHR^{61})_sNR^{34}-$ can be combined with linker L1, L2, L3, L7, L8 or L9;
- $-(CH_2)_o(CHR^{61})_sCO-$ can be combined with linker L4, L5, L6, L10, L11 or L12;
- 20 $-(CH_2)_p(CHR^{61})_sCO-$ can be combined with linker L4, L5, L6, L10, L11 or L12;
- $-(CH_2)_q(CHR^{61})_sCO-$ can be combined with linker L4, L5, L6, L10, L11 or L12;
- $-(CH_2)_r(CHR^{61})_sCO-$ can be combined with linker L4, L5, L6, L10, L11 or L12;
- $-(CHR^{61})_sCO-$ can be combined with linker L4, L5, L6, L10, L11 or L12;
- $-(CH_2)_m(CHR^{61})_sO-$ can be combined with linker L13 or L14 and the resulting combination
- 25 with
- $-(CH_2)_m(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;
- $-(CH_2)_o(CHR^{61})_sO-$ can be combined with linker L13 or L14 and the resulting combination
- with
- $-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;
- 30 $-(CH_2)_p(CHR^{61})_sO-$ can be combined with linker L13 or L14 and the resulting combination
- with
- $-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;
- $-(CH_2)_q(CHR^{61})_sO-$ can be combined with linker L13 or L14 and the resulting combination
- with
- 35 $-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;
- $-(CHR^{61})_sO-$ can be combined with linker L13 or L14 and the resulting combination with
- $-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_m(CHR^{61})_sS-$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_o(CHR^{61})_sS-$ can be combined with linker L13 or L14 and the resulting combination

5 with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_p(CHR^{61})_sS-$ can be combined with linker L13 or L14 and the resulting combination

with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

10 $-(CH_2)_q(CHR^{61})_sS-$ can be combined with linker L13 or L14 and the resulting combination

with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CHR^{61})_sS-$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

15 $-(CH_2)_m(CHR^{61})_sNR^{34}$ can be combined with linker L13 or L14 and the resulting

combination with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_o(CHR^{61})_sNR^{34}$ can be combined with linker L13 or L14 and the resulting combination

with

20 $-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_p(CHR^{61})_sNR^{34}$ can be combined with linker L13 or L14 and the resulting combination

with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_q(CHR^{61})_sNR^{34}$ can be combined with linker L13 or L14 and the resulting combination

25 with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CHR^{61})_sNR^{34}$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_o(CHR^{61})_sCO-$ can be combined with linker L15 or L16 and the resulting combination

30 with

$-(CH_2)_m(CHR^{61})_sX-$; $-(CH_2)_o(CHR^{61})_sX-$; $-(CH_2)_p(CHR^{61})_sX-$; $-(CH_2)_q(CHR^{61})_sX-$; or $-(CHR^{61})_sX-$;

$-(CH_2)_p(CHR^{61})_sCO-$ can be combined with linker L15 or L16 and the resulting combination

with

35 $-(CH_2)_m(CHR^{61})_sX-$; $-(CH_2)_o(CHR^{61})_sX-$; $-(CH_2)_p(CHR^{61})_sX-$; $-(CH_2)_q(CHR^{61})_sX-$; or

$-(CHR^{61})_sX-$;

$-(CH_2)_q(CHR^{61})_sCO-$ can be combined with linker L15 or L16 and the resulting combination with

$-(CH_2)_m(CHR^{61})_sX-$, $-(CH_2)_o(CHR^{61})_sX-$, $-(CH_2)_p(CHR^{61})_sX-$, $-(CH_2)_q(CHR^{61})_sX-$; or $-(CHR^{61})_sX-$;

5 $-(CH_2)_r(CHR^{61})_sCO-$ can be combined with linker L15 or L16 and the resulting combination with

$-(CH_2)_m(CHR^{61})_sX-$, $-(CH_2)_o(CHR^{61})_sX-$, $-(CH_2)_p(CHR^{61})_sX-$, $-(CH_2)_q(CHR^{61})_sX-$; or $-(CHR^{61})_sX-$;

10 $-(CHR^{61})_sCO-$ can be combined with linker L15 or L16 and the resulting combination with $-(CH_2)_m(CHR^{61})_sX-$; $-(CH_2)_o(CHR^{61})_sX-$; $-(CH_2)_p(CHR^{61})_sX-$; $-(CH_2)_q(CHR^{61})_sX-$; or $-(CHR^{61})_sX-$;

15 Z , Z^1 and Z^2 independently are chains of n α -amino acid residues, n being an integer from 8 to 16, the positions of said amino acid residues in said chains being counted starting from the N-terminal amino acid, whereby these amino acid residues are, depending on their position in the chains, Gly, or Pro, or of formula $-A-CO-$, or of formula $-B-CO-$, or of one of the types

C: $-NR^{20}CH(R^{72})CO-$;

D: $-NR^{20}CH(R^{73})CO-$;

E: $-NR^{20}CH(R^{74})CO-$;

20 F: $-NR^{20}CH(R^{84})CO-$; and

H: $-NR^{20}-CH(CO-)-(CH_2)_{4-7}-CH(CO-)-NR^{20}-$;

$-NR^{20}-CH(CO-)-(CH_2)_pSS(CH_2)_p-CH(CO-)-NR^{20}-$;

$-NR^{20}-CH(CO-)-(-(CH_2)_pNR^{20}CO(CH_2)_p-CH(CO-)-NR^{20}-$; and

$-NR^{20}-CH(CO-)-(-(CH_2)_pNR^{20}CONR^{20}(CH_2)_p-CH(CO-)-NR^{20}-$;

25 R^{71} is H; lower alkyl; lower alkenyl; $-(CH_2)_p(CHR^{61})_sOR^{75}$; $-(CH_2)_p(CHR^{61})_sSR^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sCOOR^{75}$; $-(CH_2)_pCONR^{58}R^{59}$; $-(CH_2)_pPO(OR^{62})_2$; $-(CH_2)_pSO_2R^{62}$; or $-(CH_2)_o-C_6R^{67}R^{68}R^{69}R^{70}R^{76}$;

R^{72} is H; lower alkyl; lower alkenyl; $-(CH_2)_p(CHR^{61})_sOR^{85}$; or $-(CH_2)_p(CHR^{61})_sSR^{85}$;

30 R^{73} is $-(CH_2)_oR^{77}$; $-(CH_2)_oO(CH_2)_oR^{77}$; $-(CH_2)_oS(CH_2)_oR^{77}$; or $-(CH_2)_rNR^{20}(CH_2)_oR^{77}$;

R^{74} is $-(CH_2)_pNR^{78}R^{79}$; $-(CH_2)_pNR^{77}R^{80}$; $-(CH_2)_pC(=NR^{80})NR^{78}R^{79}$; -

$(CH_2)_pC(=NOR^{50})NR^{78}R^{79}$;

$-(CH_2)_pC(=NNR^{78}R^{79})NR^{78}R^{79}$; $-(CH_2)_pNR^{80}C(=NR^{80})NR^{78}R^{79}$;

$-(CH_2)_pN=C(NR^{78}R^{80})NR^{79}R^{80}$; $-(CH_2)_pC_6H_4NR^{78}R^{79}$; $-(CH_2)_pC_6H_4NR^{77}R^{80}$;

35 $-(CH_2)_pC_6H_4C(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_pC_6H_4C(=NOR^{50})NR^{78}R^{79}$;

$-(CH_2)_pC_6H_4C(=NNR^{78}R^{79})NR^{78}R^{79}$; $-(CH_2)_pC_6H_4NR^{80}C(=NR^{80})NR^{78}R^{79}$;

$-(CH_2)_pC_6H_4N=C(NR^{78}R^{80})NR^{79}R^{80}$; $-(CH_2)_oO(CH_2)_mNR^{78}R^{79}$; $-(CH_2)_oO(CH_2)_mNR^{77}R^{80}$;

- $-(CH_2)_rO(CH_2)_pC(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_rO(CH_2)_pC(=NOR^{50})NR^{78}R^{79}$;
 $-(CH_2)_rO(CH_2)_pC(=NNR^{78}R^{79})NR^{78}R^{79}$; $-(CH_2)_rO(CH_2)_mNR^{80}C(=NR^{80})NR^{78}R^{79}$;
 $-(CH_2)_rO(CH_2)_mN=C(NR^{78}R^{80})NR^{79}R^{80}$; $-(CH_2)_rO(CH_2)_pC_6H_4CNR^{78}R^{79}$;
 $-(CH_2)_rO(CH_2)_pC_6H_4C(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_rO(CH_2)_pC_6H_4C(=NOR^{50})NR^{78}R^{79}$;
5 $-(CH_2)_rO(CH_2)_pC_6H_4C(=NNR^{78}R^{79})NR^{78}R^{79}$;
 $-(CH_2)_rO(CH_2)_pC_6H_4NR^{80}C(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_rS(CH_2)_mNR^{78}R^{79}$;
 $-(CH_2)_rS(CH_2)_mNR^{77}R^{80}$; $-(CH_2)_rS(CH_2)_pC(=NR^{80})NR^{78}R^{79}$;
 $-(CH_2)_rS(CH_2)_pC(=NOR^{50})NR^{78}R^{79}$; $-(CH_2)_rS(CH_2)_pC(=NNR^{78}R^{79})NR^{78}R^{79}$;
 $-(CH_2)_rS(CH_2)_mNR^{80}C(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_rS(CH_2)_mN=C(NR^{78}R^{80})NR^{79}R^{80}$;
10 $-(CH_2)_rS(CH_2)_pC_6H_4CNR^{78}R^{79}$; $-(CH_2)_rS(CH_2)_pC_6H_4C(=NR^{80})NR^{78}R^{79}$;
 $-(CH_2)_rS(CH_2)_pC_6H_4C(=NOR^{50})NR^{78}R^{79}$; $-(CH_2)_rS(CH_2)_pC_6H_4C(=NNR^{78}R^{79})NR^{78}R^{79}$;
 $-(CH_2)_rS(CH_2)_pC_6H_4NR^{80}C(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_pNR^{80}COR^{64}$; $-(CH_2)_pNR^{80}COR^{77}$;
 $-(CH_2)_pNR^{80}CONR^{78}R^{79}$; or $-(CH_2)_pC_6H_4NR^{80}CONR^{78}R^{79}$;

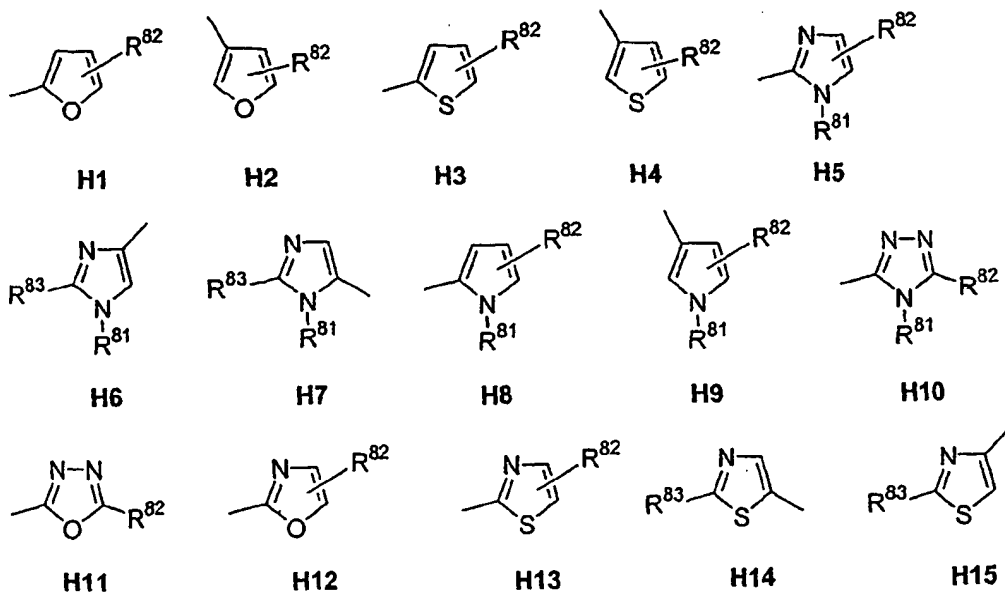
R^{75} is lower alkyl; lower alkenyl; or aryl-lower alkyl;

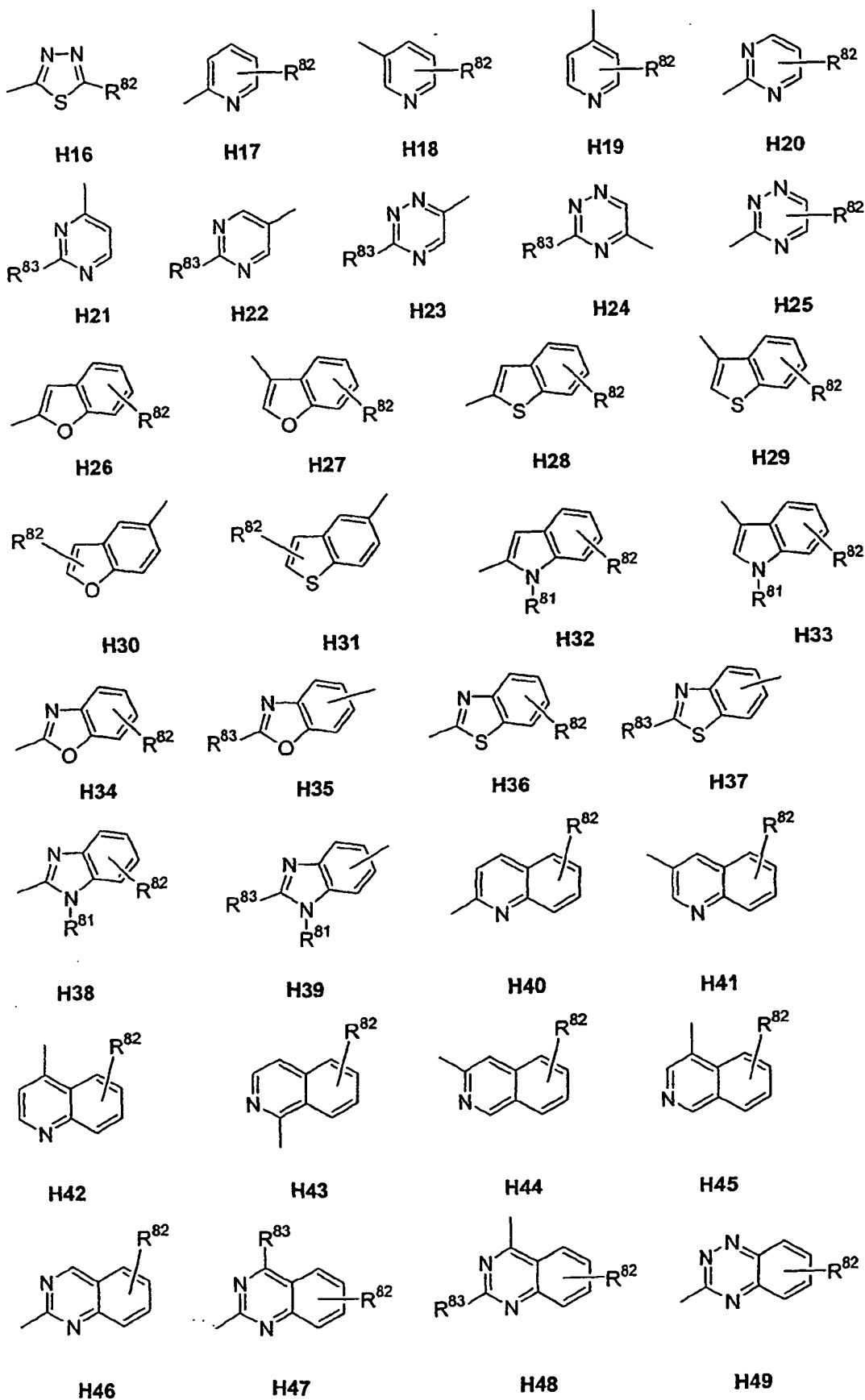
- 15 R^{33} and R^{75} taken together can form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$;

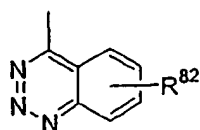
R^{75} and R^{82} taken together can form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$;

- R^{76} is H; lower alkyl; lower alkenyl; aryl-lower alkyl; $-(CH_2)_oOR^{72}$; $-(CH_2)_oSR^{72}$;
20 $-(CH_2)_oNR^{33}R^{34}$; $-(CH_2)_oOCONR^{33}R^{75}$; $-(CH_2)_oNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_oCOOR^{75}$; $-(CH_2)_oCONR^{58}R^{59}$; $-(CH_2)_oPO(OR^{60})_2$; $-(CH_2)_pSO_2R^{62}$; or
 $-(CH_2)_oCOR^{64}$;

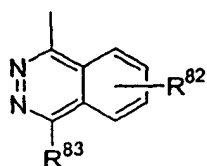
R^{77} is $-C_6R^{67}R^{68}R^{69}R^{70}R^{76}$; or a heteroaryl group of one of the formulae



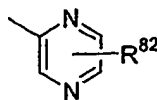




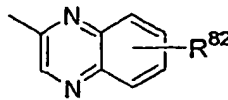
H50



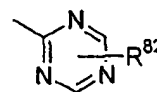
H51



H52



H53



H54

R^{78} is H; lower alkyl; aryl; or aryl-lower alkyl;

R^{78} and R^{82} taken together can form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$;

5 R^{79} is H; lower alkyl; aryl; or aryl-lower alkyl; or

R^{78} and R^{79} , taken together, can be $-(CH_2)_{2-7}-$; $-(CH_2)_2O(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$;

R^{80} is H; or lower alkyl;

R^{81} is H; lower alkyl; or aryl-lower alkyl;

R^{82} is H; lower alkyl; aryl; heteroaryl; or aryl-lower alkyl;

10 R^{33} and R^{82} taken together can form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$;

R^{83} is H; lower alkyl; aryl; or $-NR^{78}R^{79}$;

R^{84} is $-(CH_2)_m(CHR^{61})_sOH$; $-(CH_2)_pCONR^{78}R^{79}$; $-(CH_2)_pNR^{80}CONR^{78}R^{79}$; $-(CH_2)_pC_6H_4CONR^{78}R^{79}$; or $-(CH_2)_pC_6H_4NR^{80}CONR^{78}R^{79}$;

15 R^{85} is lower alkyl; or lower alkenyl;

with the proviso that in said chain(s) of n α -amino acid residues Z , Z^1 and Z^2

- if n is 8, the amino acid residues in positions 1 to 8 are:

20 - P1: of type C or of type D or of type E or of type F, or the residue is Pro;

- P2: of type E or of type D or of type F;

- P3: of type E or of type C, or the residue is Pro;

- P4: of type E or of formula $-A-CO-$;

- P5: of type E or of formula $-B-CO-$, or the residue is Gly;

25 - P6: of type D, or the residue is Pro;

- P7: of type or of type C or of type D; and

- P8: of type C or of type D or of type E or of type F, or the residue is Pro; or

P2 and P7, taken together, can form a group of type H; and at P4 and P5 also

30 D-isomers being possible;

- if n is 9, the amino acid residues in positions 1 to 9 are:
 - P1: of type C or of type D or of type E or of type F, or the residue is Pro;
 - P2: of type E or of type D or of type F;
 - 5 - P3: of type C or of type D or of type E, or the residue is Pro;
 - P4: of type E or of type D, or the residue is Pro;
 - P5: of type E, or the residue is Gly or Pro;
 - P6: of type D or of type E, or the residue is Gly or Pro;
 - P7: of type E or of type D or of type C, or the residue is Pro;
 - 10 - P8: of type E or of type D; and
 - P9: of type C or of type D or of type E or of type F, or the residue is Pro; or
 - P2 and P8, taken together, can form a group of type H; and at P4, P5 and P6 also D-isomers being possible;
- 15 - if n is 10, the amino acid residues in positions 1 to 10 are:
 - P1: of type C or of type D or of type E or of type F, or the residue is Pro;
 - P2: of type E or of type D, or the residue is Pro;
 - 20 - P3: of type C or of type E;
 - P4: of type E or of type D or of type F, or the residue is Pro;
 - P5: of type E or of type F or of formula -A-CO-, or the residue is Gly;
 - P6: of type E or of formula -B-CO-, or the residue is Gly;
 - P7: of type D or of type E, or the residue is Gly or Pro;
 - 25 - P8: of type D or of type E;
 - P9: of type E or of type D or of type C, or the residue is Pro; and
 - P10: of type C or of type D or of type E or of type F; or
 - P3 and P8, taken together, can form a group of type H; and at P5 and P6 also D-isomers being possible;
- 30 - if n is 11, the amino acid residues in positions 1 to 11 are:
 - P1: of type C or of type D or of type E or of type F, or the residue is Pro;
 - P2: of type E or of type C or of type D;
 - 35 - P3: of type D or of type E, or the residue is Pro;
 - P4: of type E or of type C or of type F;
 - P5: of type E or of type F, or the residue is Gly or Pro;

- P6: of type E or of type F, or the residue is Gly or Pro;
- P7: of type E or of type F, or the residue is Gly or P ro;
- P8: of type D or of type E or of type F;
- P9: of type D or of type E, or the residue is Pro;
- 5 - P10: of type E or of type C or of type D; and
- P11: of type C or of type D or of type E or of type F, or the residue is Pro; or
- P4 and P8 and/or P2 and P10, taken together, can form a group of type H; and at P5, P6 and P7 also D-isomers being possible;

10

- if n is 12, the amino acid residues in positions 1 to 12 are:

- P1: of type C or of type D or of type E or of type F, or the residue is Pro;
- P2: of type E or of type D;
- 15 - P3: of type C or of type D, or the residue is Pro;
- P4: of type E or of type F or of type D;
- P5: of type E or of type D or of type C, or the residue is Gly or Pro;
- P6: of type E or of type F or of formula -A-CO-, or the residue is Gly;
- P7: of type E or of type F or of formula -B-CO-;
- 20 - P8: of type D or of type C, or the residue is Pro;
- P9: of type E or of type D or of type F;
- P10: of type D or of type C, or the residue is Pro;
- P11: of type E or of type D; and
- 25 - P12: of type C or of type D or of type E or of type F, or the residue is Pro; or
- P4 and P9 and/or P2 and P11, taken together, can form a group of type H; and at P6 and P7 also D-isomers being possible;

- if n is 13, the amino acid residues in positions 1 to 13 are:

- 30 - P1: of type C or of type D or of type E or of type F, or the residue is Pro;
- P2: of type E or of type F or of type D;
- P3: of type C or of type D or of type E, or the residue is Pro;
- P4: of type E of type C or of type F;
- P5: of type E or of type D, or the residue is Gly or Pro;
- 35 - P6: of type E or of type F, or the residue is Gly or Pro;
- P7: of type E or of type F, or the residue is Pro;
- P8: of type D or of type E or of type F, or the residue is Pro;

- P9: of type D or of type E, or the residue is Pro;
- P10: of type E or of type C or of type F;
- P11: of type C or of type E, or the residue is Pro;
- P12: of type E or of type D or of type C; and
- 5 - P13: of type C or of type D or of type E or of type F, or the residue is Pro; or
P4 and P10 and/or P2 and P12, taken together, can form a group of type H;
and at P6, P7 and P8 also D-isomers being possible;

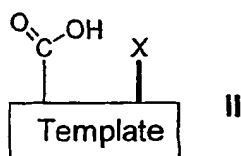
- if n is 14, the amino acid residues in positions 1 to 14 are:
- 10 - P1: of type C or of type D or of type E or of type F, or the residue is
Pro;
- P2: of type E or of type C or of type D, or the residue is Pro;
- P3: of type C or of type D or of type E;
- P4: of type D or of type C or of type E, or the residue is Pro;
- 15 - P5: of type E or of type D;
- P6: of type E or of type F, or the residue is Gly or Pro;
- P7: of type E or of type F or of formula -A-CO-, or the residue is Gly;
- P8: of type E or of type F or of formula -B-CO-, or the residue is Gly;
- P9: of type D or of type E, or the residue is Pro;
- 20 - P10: of type C or of type D or of type E;
- P11: of type E or of type D or of type F, or the residue is Pro;
- P12: of type D or of type E;
- P13: of type E or of type C or of type D, or the residue is Pro; and
- P14: of type C or of type D or of type E or of type F, or the residue is
25 Pro; or
- P5 and P10 and/or P3 and P12, taken together, can form a group of type H;
and at P7 and P8 also D-isomers being possible;

- if n is 15, the amino acid residues in positions 1 to 15 are:
- 30 P1: of type C or of type D or of type E or of type F, or the residue is
Pro;
- P2: of type E or of type F or of type D;
- P3: of type C or of type D or of type E, or the residue is Pro;
- P4: of type E or of type D or of type F;
- 35 P5: of type C or of type D or of type E, or the residue is Pro;
- P6: of type E or of type D or of type F;
- P7: of type C or of type E, or the residue is Pro;

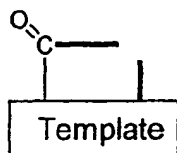
- P8: of type E or of type F, or the residue is Gly or Pro;
 P9: of type E or of type F, or the residue is Gly or Pro;
 P10: of type E or of type D;
 P11: of type C or of type D or of type E, or the residue is Pro;
 5 P12: of type E or of type C or of type F;
 P13: of type D or of type E, or the residue is Pro;
 P14: of type E or of type C or of type D; and
 P15: of type C or of type D or of type E or of type F, or the residue is
 Pro; or
 10 P6 and P10 and/or P4 and P12 and/or P2 and P14, taken together, can form a
 group of type H; and at P7, P8 and P9 also D-isomers being possible; and
- if n is 16, the amino acid residues in positions 1 to 16 are:
- 15 - P1: of type D, or of type E or of type C or of type F, or the residue is
 Pro;
 - P2: of type E or of type F or of type D;
 - P3: of type C or of type D or of type E, or the residue is Pro;
 - P4: of type E or of type D or of type F;
 - P5: of type D or of type C or of type E, or the residue is Pro;
 20 - P6: of type E or of type D;
 - P7: of type E or of type F, or the residue is Gly or Pro;
 - P8: of type E or of type F or of formula -A-CO-, or the residue is Gly;
 - P9: of type E or of formula -B-CO-, or the residue is Gly;
 - P10: of type D or of type E, or the residue is Pro;
 25 - P11: of type E or of type C or of type D;
 - P12: of type D or of type C or of type E, or the residue is Pro;
 - P13: of type E or of type C or of type F;
 - P14: of type C or of type D or of type E, or the residue is Pro;
 - P15: of type E or of type C or of type D; and
 30 - P16: of type C or of type D or of type E or of type F, or the residue is
 Pro; or
 - P6 and P11 and/or P4 and P13 and/or P2 and P15, taken together, can form a
 group of type H; and at P8 and P9 also D-isomers being possible;
- 35 and pharmaceutically acceptable salts thereof.

In accordance with the present invention these β -hairpin peptidomimetics can be prepared by a process which comprises

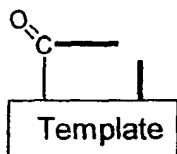
- (a) coupling an appropriately functionalized solid support with an appropriately N-protected derivative of that amino acid which in the desired end-product is in position $n/2$,
 $n/2+1$ or $n/2-1$ if n is an even number and, respectively, in position $n/2+1/2$ or $n/2-1/2$ if n is an odd number, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;
- (b) removing the N-protecting group from the product thus obtained;
- (c) coupling the product thus obtained with an appropriately N-protected derivative of that amino acid which in the desired end-product is one position nearer the N-terminal amino acid residue, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;
- (d) removing the N-protecting group from the product thus obtained;
- (e) repeating, if necessary, steps (c) and (d) until the N-terminal amino acid residue has been introduced;
- (f) coupling the product thus obtained to a compound of the general formula



wherein



- is as defined above and X is an N-protecting group or, if



is to be group (a1) or (a2), above, alternatively

- (fa) coupling the product obtained in step (d) or (e) with an appropriately N-protected derivative of an amino acid of the general formula



wherein B and A are as defined above, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

- (fb) removing the N-protecting group from the product thus obtained; and

- (fc) coupling the product thus obtained with an appropriately N-protected derivative of an amino acid of the above general formula IV and, respectively, III, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;
- 5 (g) removing the N-protecting group from the product obtained in step (f) or (fc);
- (h) coupling the product thus obtained to an appropriately N-protected derivative of that amino acid which in the desired end-product is in position n, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;
- (i) removing the N-protecting group from the product thus obtained;
- 10 (j) coupling the product thus obtained to an appropriately N-protected derivative of that amino acid which in the desired end-product is one position farther away from position n, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;
- (k) removing the N-protecting group from the product thus obtained;
- 15 (l) repeating, if necessary, steps (j) and (k) until all amino acid residues have been introduced;
- (m) if desired, selectively deprotecting one or several protected functional group(s) present in the molecule and appropriately substituting the reactive group(s) thus liberated;
- (o) detaching the product thus obtained from the solid support;
- 20 (p) cyclizing the product cleaved from the solid support;
- (q) if, desired
- (qa) forming one or several interstrand linkage(s) between side-chains of appropriate amino acid residues at opposite positions of the β -strand region; and/or
- (qb) connecting two building blocks of the type of formula Ia via a bridge
- 25 -G1 - L - G2-;
- (r) removing any protecting groups present on functional groups of any members of the chain of amino acid residues and, if desired, any protecting group(s) which may in addition be present in the molecule; and
- (s) if desired, converting the product thus obtained into a pharmaceutically acceptable salt
- 30 or converting a pharmaceutically acceptable, or unacceptable, salt thus obtained into the corresponding free compound of formula I or into a different, pharmaceutically acceptable, salt.

The peptidomimetics of the present invention can also be enantiomers of the compounds of

35 formulae Ia and Ib. These enantiomers can be prepared by a modification of the above process in which enantiomers of all chiral starting materials are used.

As used in this description, the term "alkyl", taken alone or in combinations, designates saturated, straight-chain or branched hydrocarbon radicals having up to 24, preferably up to 12, carbon atoms. Similarly, the term "alkenyl" designates straight chain or branched hydrocarbon radicals having up to 24, preferably up to 12, carbon atoms and containing at least one or, depending on the chain length, up to four olefinic double bonds. The term "lower" designates radicals and compounds having up to 6 carbon atoms. Thus, for example, the term "lower alkyl" designates saturated, straight-chain or branched hydrocarbon radicals having up to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, sec.-butyl, isobutyl, tert.-butyl and the like. The term "aryl" designates aromatic carbocyclic hydrocarbon radicals containing one or two six-membered rings, such as phenyl or naphthyl, which may be substituted by up to three substituents such as Br, Cl, F, CF₃, NO₂, lower alkyl or lower alkenyl. The term "heteroaryl" designates aromatic heterocyclic radicals containing one or two five- and/or six-membered rings, at least one of them containing up to three heteroatoms selected from the group consisting of O, S and N and said ring(s) being optionally substituted; representative examples of such optionally substituted heteroaryl radicals are indicated hereinabove in connection with the definition of R⁷⁷.

The structural element -A-CO- designates amino acid building blocks which in combination with the structural element -B-CO- form templates (a1) and (a2). Templates (a) through (p) constitute building blocks which have an N-terminus and a C-terminus oriented in space in such a way that the distance between those two groups may lie between 4.0-5.5Å. A peptide chain Z, Z¹ or Z² is linked to the C-terminus and the N-terminus of the templates (a) through (p) via the corresponding N- and C-termini so that the template and the chain form a cyclic structure such as that depicted in formula Ia. In a case as here where the distance between the N- and C- termini of the template lies between 4.0-5.5Å the template will induce the H-bond network necessary for the formation of a β -hairpin conformation in the peptide chain Z, Z¹ or Z². Thus template and peptide chain form a *β -hairpin mimetic*. The β -hairpin mimetics can also be coupled through groups G1 and G2 and a linker unit L to form the dimeric constructs of formula Ib.

The β -hairpin conformation is highly relevant for the antibiotic and anticancer activities of the β -hairpin mimetics of the present invention. The β -hairpin stabilizing conformational properties of the templates (a) through (p) play a key role not only for antibiotic and anticancer activity but also for the synthesis process defined hereinabove, as incorporation of

the templates near the middle of the linear protected peptide precursors enhance significantly cyclization yields.

Building blocks A1-A69 belong to a class of amino acids wherein the N-terminus is a secondary amine forming part of a ring. Among the genetically encoded amino acids only proline falls into this class. The configuration of building block A1 through A69 is (D), and they are combined with a building block -B-CO- of (L)-configuration. Preferred combinations for templates (a1) are $^D\text{A1-CO-}^L\text{B-CO-}$ to $^D\text{A69-CO-}^L\text{B-CO-}$. Thus, for example, $^D\text{Pro-}^L\text{Pro}$ constitutes the prototype of templates (a1). Less preferred, but possible are combinations where templates (a2) are $^L\text{A1-CO-}^D\text{B-CO-}$ to $^L\text{A69-CO-}^D\text{B-CO-}$. Thus, for example, $^L\text{Pro-}^D\text{Pro}$ constitutes a less preferred prototype of template (a2).

It will be appreciated that building blocks -A1-CO- to -A69-CO- in which A has (D)-configuration, are carrying a group R^1 at the α -position to the N-terminus. The preferred values for R^1 are H and lower alkyl with the most preferred values for R^1 being H and methyl. It will be recognized by those skilled in the art, that A1-A69 are shown in (D)-configuration which, for R^1 being H and methyl, corresponds to the (R)-configuration. Depending on the priority of other values for R^1 according to the Cahn, Ingold and Prelog-rules, this configuration may also have to be expressed as (S).

In addition to R^1 building blocks -A1-CO- to -A69-CO- can carry an additional substituent designated as R^2 to R^{17} . This additional substituent can be H, and if it is other than H, it is preferably a *small to medium-sized aliphatic or aromatic* group. Examples of preferred values for R^2 to R^{17} are:

R^2 : H; lower alkyl; lower alkenyl; $(\text{CH}_2)_m\text{OR}^{55}$ (where R^{55} : lower alkyl; or lower alkenyl); $(\text{CH}_2)_m\text{SR}^{56}$ (where R^{56} : lower alkyl; or lower alkenyl); $(\text{CH}_2)_m\text{NR}^{33}\text{R}^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; R^{33} and R^{34} taken together form: $-(\text{CH}_2)_{2-6}$; $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2$; $-(\text{CH}_2)_2\text{S}(\text{CH}_2)_2$; or $-(\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_2$; R^{57} : H; or lower alkyl); $(\text{CH}_2)_m\text{OCONR}^{33}\text{R}^{75}$ (where R^{33} : H; or lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(\text{CH}_2)_{2-6}$; $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2$; $-(\text{CH}_2)_2\text{S}(\text{CH}_2)_2$; or $-(\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_2$; where R^{57} : H; or lower alkyl); $-(\text{CH}_2)_m\text{NR}^{20}\text{CONR}^{33}\text{R}^{82}$ (where R^{20} : H; or lower lower alkyl; R^{33} : H; or lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(\text{CH}_2)_{2-6}$; $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2$; $-(\text{CH}_2)_2\text{S}(\text{CH}_2)_2$; or $-(\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_2$; where R^{57} : H; or lower alkyl); $-(\text{CH}_2)_6\text{N}(\text{R}^{20})\text{COR}^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl); $-(\text{CH}_2)_6\text{COOR}^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(\text{CH}_2)_6\text{CONR}^{58}\text{R}^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(\text{CH}_2)_{2-6}$; $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2$; $-(\text{CH}_2)_2\text{S}(\text{CH}_2)_2$;

; or

alkyl; or lower alkenyl); $-(CH_2)_6SO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).

5 - R^3 : H; lower alkyl; lower alkenyl; $-(CH_2)_mOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl); $-(CH_2)_mSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl); $-(CH_2)_mNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} : H; or lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or lower alkyl; R^{33} : H; or lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_nN(R^{20})COR^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl); $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).

R^4 : H; lower alkyl; lower alkenyl; $-(CH_2)_mOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl); $-(CH_2)_mSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl); $-(CH_2)_mNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} : H; or lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or lower lower alkyl; R^{33} : H; or lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_mN(R^{20})COR^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl); $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower

35 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_6PO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl); $-(CH_2)_6SO_2R^{62}$ (where R^{62} : lower alkyl; or lower

alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).

- R^5 : lower alkyl; lower alkenyl; $-(CH_2)_oOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl); $-(CH_2)_oSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl); $-(CH_2)_oNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_oOCONR^{33}R^{75}$ (where R^{33} : H; or lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; R^{57} : where H; or lower alkyl); $(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or lower lower alkyl; R^{33} : H; or lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $(CH_2)_oN(R^{20})COR^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : alkyl; alkenyl; aryl; and aryl-lower alkyl; heteroaryl-lower alkyl); $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
- R^6 : H; lower alkyl; lower alkenyl; $-(CH_2)_oOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl); $-(CH_2)_oSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl); $-(CH_2)_oNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_oOCONR^{33}R^{75}$ (where R^{33} : H; or lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or lower lower alkyl; R^{33} : H; or lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_oN(R^{20})COR^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl); $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).

- R^7 : lower alkyl; lower alkenyl; $-(CH_2)_qOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl); $-(CH_2)_qSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl); $-(CH_2)_qNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_{2-}$; $-(CH_2)_2S(CH_2)_{2-}$; or $-(CH_2)_2NR^{57}(CH_2)_{2-}$; where R^{57} : H; or lower alkyl); $-(CH_2)_qOCONR^{33}R^{75}$ (where R^{33} : H; or lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_{2-}$; $-(CH_2)_2S(CH_2)_{2-}$; or $-(CH_2)_2NR^{57}(CH_2)_{2-}$; where R^{57} : H; or lower alkyl); $(CH_2)_qNR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or lower lower alkyl; R^{33} : H; or lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_{2-}$; $-(CH_2)_2S(CH_2)_{2-}$; or $-(CH_2)_2NR^{57}(CH_2)_{2-}$; where R^{57} : H; or lower alkyl); $-(CH_2)_qN(R^{20})COR^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl); $-(CH_2)_rCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(CH_2)_qCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_{2-}$; $-(CH_2)_2S(CH_2)_{2-}$; or $-(CH_2)_2NR^{57}(CH_2)_{2-}$; where R^{57} : H; or lower alkyl); $-(CH_2)_rPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl); $(CH_2)_sSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
- R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; $-(CH_2)_oOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl); $(CH_2)_oSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl); $-(CH_2)_oNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_{2-}$; $-(CH_2)_2S(CH_2)_{2-}$; or $-(CH_2)_2NR^{57}(CH_2)_{2-}$; where R^{57} : H; or lower alkyl); $-(CH_2)_oOCONR^{33}R^{75}$ (where R^{33} : H; or lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_{2-}$; $-(CH_2)_2S(CH_2)_{2-}$; or $-(CH_2)_2NR^{57}(CH_2)_{2-}$; where R^{57} : H; or lower alkyl); $-(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or lower lower alkyl; R^{33} : H; or lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_{2-}$; $-(CH_2)_2S(CH_2)_{2-}$; or $-(CH_2)_2NR^{57}(CH_2)_{2-}$; where R^{57} : H; or lower alkyl); $-(CH_2)_oN(R^{20})COR^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl); $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_{2-}$; $-(CH_2)_2S(CH_2)_{2-}$; or $-(CH_2)_2NR^{57}(CH_2)_{2-}$; where R^{57} : H; or lower alkyl); $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
- R^9 : lower alkyl; lower alkenyl; $-(CH_2)_oOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl); $-(CH_2)_oSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl); $-(CH_2)_oNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form:

- $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl; $-(CH_2)_6OCONR^{33}R^{75}$ (where R^{33} : H; or lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or lower lower alkyl; R^{33} : H; or lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_6N(R^{20})COR^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl); $-(CH_2)_6COOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(CH_2)_6CONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_6PO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl); $-(CH_2)_6SO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
- R^{10} : lower alkyl; lower alkenyl; $-(CH_2)_6OR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl); $-(CH_2)_6SR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl); $-(CH_2)_6NR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_6OCONR^{33}R^{75}$ (where R^{33} : H; or lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_6NR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or lower lower alkyl; R^{33} : H; or lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_6N(R^{20})COR^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl); $-(CH_2)_6COOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(CH_2)_6CONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_6PO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl); $-(CH_2)_6SO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
- R^{11} : H; lower alkyl; lower alkenyl; $-(CH_2)_mOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl); $-(CH_2)_mSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl); $-(CH_2)_mNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} : H; or lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or

- $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or lower lower alkyl; R^{33} : H; or lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_mN(R^{20})COR^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl); $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
- R^{12} : H; lower alkyl; lower alkenyl; $-(CH_2)_mOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl); $-(CH_2)_mSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl); $-(CH_2)_mNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} : H; or lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or lower lower alkyl; R^{33} : H; or lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_mN(R^{20})COR^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl); $-(CH_2)_rCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(CH_2)_rCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_rPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
- R^{13} : lower alkyl; lower alkenyl; $-(CH_2)_qOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl); $-(CH_2)_qSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl); $-(CH_2)_qNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_qOCONR^{33}R^{75}$ (where R^{33} : H; or lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_qNR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or lower lower alkyl; R^{33} : H; or lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or

- $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_qN(R^{20})COR^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl); $-(CH_2)_rCOO^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(CH_2)_qCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$;
- 5 or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_rPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl); $-(CH_2)_rSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
- R^{14} : H; lower alkyl; lower alkenyl; $-(CH_2)_mOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl); $-(CH_2)_mSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl); $-(CH_2)_mNR^{33}R^{34}$ (where
- 10 R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} : H; or lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or
- 15 $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or lower lower alkyl; R^{33} : H; or lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or
- $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_mN(R^{20})COR^{64}$ (where: R^{20} : H; lower alkyl; R^{64} : lower alkyl; or lower alkenyl); $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; or
- 20 lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
- 25 - R^{15} : lower alkyl; lower alkenyl; $-(CH_2)_oOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl); $-(CH_2)_oSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl); $-(CH_2)_oNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form:
- $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_oOCONR^{33}R^{75}$ (where R^{33} : H; or lower alkyl; or lower alkenyl; R^{75} : lower alkyl;
- 30 or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or lower lower alkyl; R^{33} : H; or lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or
- $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_oN(R^{20})COR^{64}$ (where: R^{20} : H; or
- 35 lower alkyl; R^{64} : lower alkyl; or lower alkenyl); particularly favoured are $NR^{20}CO$ lower alkyl ($R^{20}=H$; or lower alkyl); $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; lower alkyl; or R^{58}

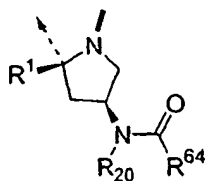
and R⁵⁹ taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R⁵⁷: H; or lower alkyl; $-(CH_2)_6PO(OR^{60})_2$ (where R⁶⁰: lower alkyl; or lower alkenyl); $-(CH_2)_6SO_2R^{62}$ (where R⁶²: lower alkyl; or lower alkenyl); or $-(CH_2)_6C_6H_4R^8$ (where R⁸: H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy).

5 - R^{16} : lower alkyl; lower alkenyl; $-(CH_2)_oOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl); $-(CH_2)_oSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl); $-(CH_2)_oNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_oOCONR^{33}R^{75}$ (where R^{33} : H; or lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or lower lower alkyl; R^{33} : H; or lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_oN(R^{20})COR^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl); $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).

- R^{17} : lower alkyl; lower alkenyl; $-(CH_2)_qOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl); $-(CH_2)_qSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl); $-(CH_2)_qR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_qCONR^{33}R^{75}$ (where R^{33} : H; or lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_qNR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or lower lower alkyl; R^{33} : H; or lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_qN(R^{20})COR^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl); $-(CH_2)_rCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(CH_2)_qCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_rPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl); $-(CH_2)_sSO_2R^{62}$ (where R^{62} : lower alkyl; or lower

alkenyl); or $-(CH_2)_4C_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).

- Among the building blocks A1 to A69 the following are preferred: A5 with R^2 being H, A8, A22, A25, A38 with R^2 being H, A42, A47, and A50. Most preferred are building blocks of type A8':



A8'

- wherein R^{20} is H or lower alkyl; and R^{64} is alkyl; alkenyl; aryl; aryl-lower alkyl; or heteroaryl-lower alkyl; especially those wherein R^{64} is n-hexyl (A8'-1); n-heptyl (A8'-2); 4-(phenyl)benzyl (A8'-3); diphenylmethyl (A8'-4); 3-amino-propyl (A8'-5); 5-amino-pentyl (A8'-6); methyl (A8'-7); ethyl (A8'-8); isopropyl (A8'-9); isobutyl (A8'-10); n-propyl (A8'-11); cyclohexyl (A8'-12); cyclohexylmethyl (A8'-13); n-butyl (A8'-14); phenyl (A8'-15); benzyl (A8'-16); (3-indolyl)methyl (A8'-17); 2-(3-indolyl)ethyl (A8'-18); (4-phenyl)phenyl (A8'-19); and n-nonyl (A8'-20).

- Building block A70 belongs to the class of open-chained α -substituted α -amino acids, building blocks A71 and A72 to the corresponding β -amino acid analogues and building blocks A73-A104 to the cyclic analogues of A70. Such amino acid derivatives have been shown to constrain small peptides in well defined reverse turn or U-shaped conformations (C. M. Venkatachalam, *Biopolymers*, 1968, 6, 1425-1434; W. Kabsch, C Sander, *Biopolymers* 1983, 22, 2577). Such building blocks or templates are ideally suited for the stabilization of β -hairpin conformations in peptide loops (D. Obrecht, M. Altorfer, J. A. Robinson, "Novel Peptide Mimetic Building Blocks and Strategies for Efficient Lead Finding", *Adv. Med Chem.* 1999, Vol.4, 1-68; P. Balaram, "Non-standard amino acids in peptide design and protein engineering", *Curr. Opin. Struct. Biol.* 1992, 2, 845-851; M. Crisma, G. Valle, C. Toniolo, S. Prasad, R. B. Rao, P. Balaram, " β -turn conformations in crystal structures of model peptides containing α,α -disubstituted amino acids", *Biopolymers* 1995, 35, 1-9; V. J. Hruby, F. Al-Obeidi, W. Kazmierski, *Biochem. J.* 1990, 268, 249-262).

- It has been shown that both enantiomers of building blocks -A70-CO- to A104-CO- in combination with a building block -B-CO- of L-configuration can efficiently stabilize and induce β -hairpin conformations (D. Obrecht, M. Altorfer, J. A. Robinson, "Novel Peptide

- Mimetic Building Blocks and Strategies for Efficient Lead Finding", *Adv. Med Chem.* 1999, Vol.4, 1-68; D. Obrecht, C. Spiegler, P. Schönholzer, K. Müller, H. Heimgartner, F. Stierli, *Helv. Chim. Acta* 1992, 75, 1666-1696; D. Obrecht, U. Bohdal, J. Daly, C. Lehmann, P. Schönholzer, K. Müller, *Tetrahedron* 1995, 51, 10883-10900; D. Obrecht, C. Lehmann, C. Ruffieux, P. Schönholzer, K. Müller, *Helv. Chim. Acta* 1995, 78, 1567-1587; D. Obrecht, U. Bohdal, C. Broger, D. Bur, C. Lehmann, R. Ruffieux, P. Schönholzer, C. Spiegler, *Helv. Chim. Acta* 1995, 78, 563-580; D. Obrecht, H. Karajiannis, C. Lehmann, P. Schönholzer, C. Spiegler, *Helv. Chim. Acta* 1995, 78, 703-714).
- 10 Thus, for the purposes of the present invention templates (a1) can also consist of -A70-CO- to A104-CO- where building block A70 to A104 is of either (D)- or (L)-configuration, in combination with a building block -B-CO- of (L)- configuration.
- Preferred values for R^{20} in A70 to A104 are H or lower alkyl with methyl being most preferred. Preferred values for R^{18} , R^{19} and R^{21} - R^{29} in building blocks A70 to A104 are the following:
- R^{18} : lower alkyl.
 - R^{19} : lower alkyl; lower alkenyl; $-(CH_2)_pOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl); $-(CH_2)_pSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl); $-(CH_2)_pNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_pOCONR^{33}R^{75}$ (where R^{33} : H; or lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_pNR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or lower lower alkyl; R^{33} : H; or lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_pN(R^{20})COR^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl); $-(CH_2)_pCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(CH_2)_pCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_pPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl); $-(CH_2)_pSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or $-(CH_2)_oC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
 - R^{21} : H; lower alkyl; lower alkenyl; $-(CH_2)_oOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl); $-(CH_2)_oSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl); $-(CH_2)_oNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form:

$-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl; $-(CH_2)_6OCONR^{33}R^{75}$ (where R^{33} : H; or lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_6NR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or lower lower alkyl; R^{33} : H; or lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_6N(R^{20})COR^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl); $-(CH_2)_6COOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(CH_2)_6CONR^{58}R^{59}$ (where R^{58} : lower alkyl, or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_6PO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl); $(CH_2)_6SO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or $(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).

R^{22} : lower alkyl; lower alkenyl; $-(CH_2)_6OR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl); $-(CH_2)_6SR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl); $-(CH_2)_6NR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_6OCONR^{33}R^{75}$ (where R^{33} : H; or lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_6NR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or lower lower alkyl; R^{33} : H; or lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_6N(R^{20})COR^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl); $-(CH_2)_6COOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(CH_2)_6CONR^{58}R^{59}$ (where R^{58} : lower alkyl, or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_6PO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl); $-(CH_2)_6SO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).

R^{23} : H; lower alkyl; lower alkenyl; $-(CH_2)_6OR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl); $-(CH_2)_6SR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl); $-(CH_2)_6NR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_6OCONR^{33}R^{75}$ (where R^{33} : H; or lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or

- $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_6NR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or lower lower alkyl; R^{33} : H; or lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or
 $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_6N(R^{20})COR^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl); particularly favoured are $NR^{20}CO$ lower alkyl (R^{20} =H; or lower alkyl); $-(CH_2)_6COOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl);
 $-(CH_2)_6CONR^{58}R^{59}$ (where R^{58} : lower alkyl, or lower alkenyl; and R^{59} : H; lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or
 $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_6PO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl); $-(CH_2)_6SO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or
 $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy);
 $-R^{24}$: lower alkyl; lower alkenyl; $-(CH_2)_6OR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl); $-(CH_2)_6SR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl); $-(CH_2)_6NR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form:
 $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_6OCONR^{33}R^{75}$ (where R^{33} : H; or lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or
 $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_6NR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or lower lower alkyl; R^{33} : H; or lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or
 $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_6N(R^{20})COR^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl); particularly favoured are $NR^{20}CO$ lower alkyl (R^{20} =H; or lower alkyl); $-(CH_2)_6COOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl);
 $-(CH_2)_6CONR^{58}R^{59}$ (where R^{58} : lower alkyl, or lower alkenyl; and R^{59} : H; lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or
 $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_6PO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl); $-(CH_2)_6SO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or
 $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy);
 $-R^{25}$: H; lower alkyl; lower alkenyl; $-(CH_2)_mOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl); $-(CH_2)_mNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or
 $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} : H; or lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl);
 $-(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or lower lower alkyl; R^{33} : H; or lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}-$;
 $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl);

- $-(CH_2)_mN(R^{20})COR^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl);
 $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} :
 lower alkyl; or lower alkenyl; and R^{59} : H; lower alkyl; or R^{58} and R^{59} taken together form:
 $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower
 5 alkyl); $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where
 R^{62} : lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl;
 lower alkenyl; or lower alkoxy).
 - R^{26} : H; lower alkyl; lower alkenyl; $-(CH_2)_mOR^{55}$ (where R^{55} : lower alkyl; or lower
 alkenyl); $-(CH_2)_mNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or
 10 R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or
 $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} : H; or
 lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}$;
 $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl);
 $-(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or lower lower alkyl; R^{33} : H; or lower alkyl; or lower
 15 alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}$;
 $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl);
 $-(CH_2)_mN(R^{20})COR^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl);
 $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} :
 lower alkyl; or lower alkenyl; and R^{59} : H; lower alkyl; or R^{58} and R^{59} taken together form:
 20 $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower
 alkyl); $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where
 R^{62} : lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl;
 lower alkenyl; or lower alkoxy).
 - Alternatively, R^{25} and R^{26} taken together can be $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$;
 25 $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl).
 - R^{27} : H; lower alkyl; lower alkenyl; $-(CH_2)_oOR^{55}$ (where R^{55} : lower alkyl; or lower
 alkenyl); $-(CH_2)_oSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl); $-(CH_2)_oNR^{33}R^{34}$ (where R^{33} :
 lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form:
 $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower
 30 alkyl); $-(CH_2)_oOCONR^{33}R^{75}$ (where R^{33} : H; or lower alkyl; or lower alkenyl; R^{75} : lower alkyl;
 or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or
 $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or
 lower lower alkyl; R^{33} : H; or lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{33} and
 R^{82} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or
 35 $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_oN(R^{20})COR^{64}$ (where: R^{20} : H; or
 lower alkyl; R^{64} : lower alkyl; or lower alkenyl); $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or
 lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H;

- lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl; $-(CH_2)_6PO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl); $-(CH_2)_6SO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
- 5 R^{28} : lower alkyl; lower alkenyl; $-(CH_2)_6OR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl); $-(CH_2)_6SR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl); $-(CH_2)_6NR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_6OCONR^{33}R^{75}$ (where R^{33} : H; or lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_6NR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or lower lower alkyl; R^{33} : H; or lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or
- 10 $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_6N(R^{20})COR^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl); $-(CH_2)_6COOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(CH_2)_6CONR^{58}R^{59}$ (where R^{58} : lower alkyl, or lower alkenyl; and R^{59} : H; lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_6PO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl); $-(CH_2)_6SO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
- 15 R^{29} : lower alkyl; lower alkenyl; $-(CH_2)_6OR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl); $-(CH_2)_6SR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl); $-(CH_2)_6NR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_6OCONR^{33}R^{75}$ (where R^{33} : H; or lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_6NR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or lower lower alkyl; R^{33} : H; or lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or
- 20 $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_6N(R^{20})COR^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl); particularly favored are $NR^{20}CO$ lower-alkyl ($R^{20}=H$; or lower alkyl); $-(CH_2)_6COOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl);
- 25 $-(CH_2)_6CONR^{58}R^{59}$ (where R^{58} : lower alkyl, or lower alkenyl; and R^{59} : H; lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_6PO(OR^{60})_2$ (where R^{60} : lower
- 30 $-(CH_2)_6CONR^{58}R^{59}$ (where R^{58} : lower alkyl, or lower alkenyl; and R^{59} : H; lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_6PO(OR^{60})_2$ (where R^{60} : lower
- 35 $-(CH_2)_6CONR^{58}R^{59}$ (where R^{58} : lower alkyl, or lower alkenyl; and R^{59} : H; lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_6PO(OR^{60})_2$ (where R^{60} : lower

alkyl; or lower alkenyl); $-(CH_2)_6SO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or $-(CH_2)_4C_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).

For templates (b) to (p), such as (b1) and (c1), the preferred values for the various symbols are the following:

- 5
- R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; $-(CH_2)_6OR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl); $-(CH_2)_6SR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl); $-(CH_2)_6NR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_2-6-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_6OCONR^{33}R^{75}$ (where R^{33} : H; or lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_2-6-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_6NR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or lower lower alkyl; R^{33} : H; or lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_2-6-$;
15 $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_6N(R^{20})COR^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl); $-(CH_2)_6COOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(CH_2)_6CONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; or lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_2-6-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower
20 alkyl); $-(CH_2)_6PO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl); $-(CH_2)_6SO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or $-(CH_2)_4C_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
- R^{20} : H; or lower alkyl.
- R^{30} : H, methyl.
- 25
- R^{31} : H; lower alkyl; lower alkenyl; $-(CH_2)_pOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl); $-(CH_2)_pNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_2-6-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_pOCONR^{33}R^{75}$ (where R^{33} : H; or lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_2-6-$;
30 $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_pNR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or lower lower alkyl; R^{33} : H; or lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_2-6-$;
35 $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower alkyl); $-(CH_2)_pN(R^{20})COR^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl); $-(CH_2)_6COOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(CH_2)_6CONR^{58}R^{59}$ (where R^{58} : lower alkyl, or lower alkenyl; and R^{59} : H; lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_2-6-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} : H; or lower

alkyl); $-(CH_2)_6PO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl); $-(CH_2)_6SO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or $-(CH_2)_6C_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy); most preferred is $-CH_2CONR^{58}R^{59}$ (R^{58} : H; or lower alkyl; R^{59} : lower alkyl; or lower alkenyl).

5 R^{32} : H, methyl.

R^{33} : lower alkyl; lower alkenyl; $-(CH_2)_mOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl); $-(CH_2)_mNR^{34}R^{63}$ (where R^{34} : lower alkyl; or lower alkenyl; R^{63} : H; or lower alkyl; or R^{34} and R^{63} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $(CH_2)_mOCONR^{75}R^{82}$ (where R^{75} : lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{75} and R^{82} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_mNR^{20}CONR^{78}R^{82}$ (where R^{20} : H; or lower lower alkyl; R^{78} : H; or lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{78} and R^{82} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_mN(R^{20})COR^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl); $-(CH_2)_6COOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(CH_2)_6CONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl).

20 R^{34} : H; or lower alkyl.

R^{35} : H; lower alkyl; lower alkenyl; $-(CH_2)_mOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl); $-(CH_2)_mNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} : H; or lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or lower lower alkyl; R^{33} : H; or lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_mN(R^{20})COR^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl); $-(CH_2)_6COOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(CH_2)_6CONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl).

35 R^{36} : lower alkyl; lower alkenyl; or aryl-lower alkyl.

R^{37} : H; lower alkyl; lower alkenyl; $-(CH_2)_pOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl); $-(CH_2)_pNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or

- R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl; $-(CH_2)_pOCONR^{33}R^{75}$ (where R^{33} : H; or lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl);
- 5 $-(CH_2)_pNR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or lower alkyl; R^{33} : H; or lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_pN(R^{20})COR^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl); $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} :
- 10 lower alkyl, or lower alkenyl; and R^{59} : H; lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
- 15 $-R^{38}$: H; lower alkyl; lower alkenyl; $-(CH_2)_pOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl); $-(CH_2)_pNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_pOCONR^{33}R^{75}$ (where R^{33} : H; or lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}$;
- 20 $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_pNR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or lower lower alkyl; R^{33} : H; or lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_pN(R^{20})COR^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl);
- 25 $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} : lower alkyl, or lower alkenyl; and R^{59} : H; lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl;
- 30 lower alkenyl; or lower alkoxy).
- R^{39} : H; lower alkyl; lower alkenyl; $-(CH_2)_mOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl); $-(CH_2)_mN(R^{20})COR^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl); $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; lower alkyl; or R^{58} and R^{59} taken
- 35 together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl).
- R^{40} : lower alkyl; lower alkenyl; or aryl-lower alkyl.

- R^{41} : H; lower alkyl; lower alkenyl; $-(CH_2)_pOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl); $-(CH_2)_pNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_pOCONR^{33}R^{75}$ (where R^{33} : H; or lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_pNR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or lower lower alkyl; R^{33} : H; or lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_pN(R^{20})COR^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl); $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} : lower alkyl, or lower alkenyl; and R^{59} : H; lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
- R^{42} : H; lower alkyl; lower alkenyl; $-(CH_2)_pOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl); $-(CH_2)_pNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_pOCONR^{33}R^{75}$ (where R^{33} : H; or lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_pNR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or lower lower alkyl; R^{33} : H; or lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_pN(R^{20})COR^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl); $-(CH_2)_oCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} : lower alkyl, or lower alkenyl; and R^{59} : H; lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} : lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
- R^{43} : H; lower alkyl; lower alkenyl; $-(CH_2)_mOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl); $-(CH_2)_mSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl); $-(CH_2)_mNR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} : H; or lower alkyl; or lower alkenyl; R^{75} : lower alkyl;

- or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl; $-(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or lower lower alkyl; R^{33} : H; or lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or
- 5 $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl; $-(CH_2)_mN(R^{20})COR^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl); $-(CH_2)_6COOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(CH_2)_6CONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H; lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_6PO(OR^{60})_2$
- 10 (where R^{60} : lower alkyl; or lower alkenyl); $-(CH_2)_6SO_2R^{62}$ (where R^{62} : lower alkyl; or lower alkenyl); or $-(CH_2)_4C_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
- R^{44} : lower alkyl; lower alkenyl; $-(CH_2)_pOR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl); $-(CH_2)_pSR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl); $-(CH_2)_pNR^{33}R^{34}$ (where R^{33} :
- 15 lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_pOCONR^{33}R^{75}$ (where R^{33} : H; or lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_pNR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or
- 20 lower lower alkyl; R^{33} : H; or lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_pN(R^{20})COR^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl); $-(CH_2)_pCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(CH_2)_pCONR^{58}R^{59}$ (where R^{58} : lower alkyl; or lower alkenyl; and R^{59} : H;
- 25 lower alkyl; or R^{58} and R^{59} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); or $-(CH_2)_6C_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
- R^{45} : H; lower alkyl; lower alkenyl; $-(CH_2)_6OR^{55}$ (where R^{55} : lower alkyl; or lower alkenyl); $-(CH_2)_6SR^{56}$ (where R^{56} : lower alkyl; or lower alkenyl); $-(CH_2)_6NR^{33}R^{34}$ (where R^{33} :
- 30 lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_6OCONR^{33}R^{75}$ (where R^{33} : H; or lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_6NR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or
- 35 lower lower alkyl; R^{33} : H; or lower alkyl; or lower alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_6N(R^{20})COR^{64}$ (where: R^{20} : H; or

lower alkyl; R⁶⁴: lower alkyl; or lower alkenyl); -(CH₂)₆COOR⁵⁷ (where R⁵⁷: lower alkyl; or lower alkenyl); -(CH₂)₆CONR⁵⁸R⁵⁹ (where R⁵⁸: lower alkyl; or lower alkenyl; and R⁵⁹: H; lower alkyl; or R⁵⁸ and R⁵⁹ taken together form: -(CH₂)₂₋₆; -(CH₂)₂O(CH₂)₂; -(CH₂)₂S(CH₂)₂; or -(CH₂)₂NR⁵⁷(CH₂)₂; where R⁵⁷: H; or lower alkyl); or -(CH₂)₅C₆H₄R⁸ (where R⁸: H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy).

- R⁴⁶: H; lower alkyl; lower alkenyl; -(CH₂)₅OR⁵⁵ (where R⁵⁵: lower alkyl; or lower alkenyl); -(CH₂)₅SR⁵⁶ (where R⁵⁶: lower alkyl; or lower alkenyl); -(CH₂)₅NR³³R³⁴ (where R³³: lower alkyl; or lower alkenyl; R³⁴: H; or lower alkyl; or R³³ and R³⁴ taken together form: -(CH₂)₂₋₆; -(CH₂)₂O(CH₂)₂; -(CH₂)₂S(CH₂)₂; or -(CH₂)₂NR⁵⁷(CH₂)₂; where R⁵⁷: H; or lower alkyl); -(CH₂)₅OCONR³³R⁷⁵ (where R³³: H; or lower alkyl; or lower alkenyl; R⁷⁵: lower alkyl; or R³³ and R⁷⁵ taken together form: -(CH₂)₂₋₆; -(CH₂)₂O(CH₂)₂; -(CH₂)₂S(CH₂)₂; or -(CH₂)₂NR⁵⁷(CH₂)₂; where R⁵⁷: H; or lower alkyl); -(CH₂)₅NR²⁰CONR³³R⁸² (where R²⁰: H; or lower lower alkyl; R³³: H; or lower alkyl; or lower alkenyl; R⁸²: H; or lower alkyl; or R³³ and R⁸² taken together form: -(CH₂)₂₋₆; -(CH₂)₂O(CH₂)₂; -(CH₂)₂S(CH₂)₂; or -(CH₂)₂NR⁵⁷(CH₂)₂; where R⁵⁷: H; or lower alkyl); -(CH₂)₅N(R²⁰)COR⁶⁴ (where: R²⁰: H; or lower alkyl; R⁶⁴: lower alkyl; or lower alkenyl); -(CH₂)₆COOR⁵⁷ (where R⁵⁷: lower alkyl; or lower alkenyl); -(CH₂)₆CONR⁵⁸R⁵⁹ (where R⁵⁸: lower alkyl; or lower alkenyl; and R⁵⁹: H; lower alkyl; or R⁵⁸ and R⁵⁹ taken together form: -(CH₂)₂₋₆; -(CH₂)₂O(CH₂)₂; -(CH₂)₂S(CH₂)₂; or -(CH₂)₂NR⁵⁷(CH₂)₂; where R⁵⁷: H; or lower alkyl); or -(CH₂)₅C₆H₄R⁸ (where R⁸: H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy).

- R⁴⁷: H; or OR⁵⁵ (where R⁵⁵: lower alkyl; or lower alkenyl).

- R⁴⁸: H; or lower alkyl.

- R⁴⁹: H; lower alkyl; -(CH₂)₆COOR⁵⁷ (where R⁵⁷: lower alkyl; or lower alkenyl); -(CH₂)₆CONR⁵⁸R⁵⁹ (where R⁵⁸: lower alkyl; or lower alkenyl; and R⁵⁹: H; lower alkyl; or R⁵⁸ and R⁵⁹ taken together form: -(CH₂)₂₋₆; -(CH₂)₂O(CH₂)₂; -(CH₂)₂S(CH₂)₂; or -(CH₂)₂NR⁵⁷(CH₂)₂; where R⁵⁷: H; or lower alkyl); or (CH₂)₅C₆H₄R⁸ (where R⁸: H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy).

- R⁵⁰: H; methyl.

- R⁵¹: H; lower alkyl; lower alkenyl; -(CH₂)_mOR⁵⁵ (where R⁵⁵: lower alkyl; or lower alkenyl); -(CH₂)_mNR³³R³⁴ (where R³³: lower alkyl; or lower alkenyl; R³⁴: H; or lower alkyl; or R³³ and R³⁴ taken together form: -(CH₂)₂₋₆; -(CH₂)₂O(CH₂)₂; -(CH₂)₂S(CH₂)₂; or -(CH₂)₂NR⁵⁷(CH₂)₂; where R⁵⁷: H; or lower alkyl); (CH₂)_mOCONR³³R⁷⁵ (where R³³: H; or lower alkyl; or lower alkenyl; R⁷⁵: lower alkyl; or R³³ and R⁷⁵ taken together form: -(CH₂)₂₋₆; -(CH₂)₂O(CH₂)₂; -(CH₂)₂S(CH₂)₂; or -(CH₂)₂NR⁵⁷(CH₂)₂; where R⁵⁷: H; or lower alkyl); -(CH₂)_mNR²⁰CONR³³R⁸² (where R²⁰: H; or lower lower alkyl; R³³: H; or lower alkyl; or lower alkenyl; R⁸²: H; or lower alkyl; or R³³ and R⁸² taken together form: -(CH₂)₂₋₆; -(CH₂)₂O(CH₂)₂; -(CH₂)₂S(CH₂)₂; or -(CH₂)₂NR⁵⁷(CH₂)₂; where R⁵⁷: H; or lower alkyl);

- $-(CH_2)_m N(R^{20})COR^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl);
 $-(CH_2)_p COOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(CH_2)_p CONR^{58}R^{59}$ (where R^{58} :
 lower alkyl; or lower alkenyl; and R^{59} : H; lower alkyl; or R^{58} and R^{59} taken together form:
 $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower
 5 alkyl); or $-(CH_2)_r C_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower
 alkoxy).
 - R^{52} : H; lower alkyl; lower alkenyl; $-(CH_2)_m OR^{55}$ (where R^{55} : lower alkyl; or lower
 alkenyl); $-(CH_2)_m NR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or
 R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or
 10 $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_m OCONR^{33}R^{75}$ (where R^{33} : H; or
 lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}$;
 $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl);
 $-(CH_2)_m NR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or lower lower alkyl; R^{33} : H; or lower alkyl; or lower
 alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}$;
 15 $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; R^{57} : H; or lower alkyl);
 $-(CH_2)_m N(R^{20})COR^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl);
 $-(CH_2)_p COOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(CH_2)_p CONR^{58}R^{59}$ (where R^{58} :
 lower alkyl; or lower alkenyl; and R^{59} : H; lower alkyl; or R^{58} and R^{59} taken together form:
 $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower
 20 alkyl); or $-(CH_2)_r C_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower
 alkoxy).
 - R^{53} : H; lower alkyl; lower alkenyl; $-(CH_2)_m OR^{55}$ (where R^{55} : lower alkyl; or lower
 alkenyl); $-(CH_2)_m NR^{33}R^{34}$ (where R^{33} : lower alkyl; or lower alkenyl; R^{34} : H; or lower alkyl; or
 R^{33} and R^{34} taken together form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or
 25 $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl); $-(CH_2)_m OCONR^{33}R^{75}$ (where R^{33} : H; or
 lower alkyl; or lower alkenyl; R^{75} : lower alkyl; or R^{33} and R^{75} taken together form: $-(CH_2)_{2-6}$;
 $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl);
 $-(CH_2)_m NR^{20}CONR^{33}R^{82}$ (where R^{20} : H; or lower lower alkyl; R^{33} : H; or lower alkyl; or lower
 alkenyl; R^{82} : H; or lower alkyl; or R^{33} and R^{82} taken together form: $-(CH_2)_{2-6}$;
 30 $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower alkyl);
 $-(CH_2)_m N(R^{20})COR^{64}$ (where: R^{20} : H; or lower alkyl; R^{64} : lower alkyl; or lower alkenyl);
 $-(CH_2)_p COOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $-(CH_2)_p CONR^{58}R^{59}$ (where R^{58} :
 lower alkyl; or lower alkenyl; and R^{59} : H; lower alkyl; or R^{58} and R^{59} taken together form:
 $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H; or lower
 35 alkyl); or $-(CH_2)_r C_6H_4R^8$ (where R^8 : H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower
 alkoxy).
 - R^{54} : lower alkyl; lower alkenyl; or aryl-lower alkyl.

Among the building blocks A70 to A104 the following are preferred: A74 with R²² being H, A75, A76, A77 with R²² being H, A78 and A79.

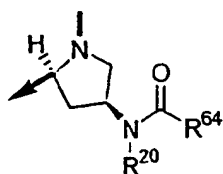
- 5 The building block -B-CO- within template (a1) and (a2) designates an L-amino acid residue. Preferred values for B are: -NR²⁰CH(R⁷¹)- and enantiomers of groups A5 with R² being H, A8, A22, A25, A38 with R² being H, A42, A47, and A50. Most preferred are

	Ala	L-Alanine
	Arg	L-Arginine
10	Asn	L-Asparagine
	Cys	L-Cysteine
	Gln	L-Glutamine
	Gly	Glycine
	His	L-Histidine
15	Ile	L-Isoleucine
	Leu	L-Leucine
	Lys	L-Lysine
	Met	L-Methionine
	Phe	L-Phenylalanine
20	Pro	L-Proline
	Ser	L-Serine
	Thr	L-Threonine
	Trp	L-Tryptophan
	Tyr	L-Tyrosine
25	Val	L-Valine
	Cit	L-Citrulline
	Orn	L-Ornithine
	tBuA	L-t-Butylalanine
	Sar	Sarcosine
30	t-BuG	L-tert.-Butylglycine
	4AmPhe	L-para-Aminophenylalanine
	3AmPhe	L-meta-Aminophenylalanine
	2AmPhe	L-ortho-Aminophenylalanine
	Phe(mC(NH ₂)=NH)	L-meta-Amidinophenylalanine
35	Phe(pC(NH ₂)=NH)	L-para-Amidinophenylalanine
	Phe(mNHC (NH ₂)=NH)	L-meta-Guanidinophenylalanine
	Phe(pNHC (NH ₂)=NH)	L-para-Guanidinophenylalanine

	Phg	L-Phenylglycine
	Cha	L-Cyclohexylalanine
	C ₄ al	L-3-Cyclobutylalanine
	C ₅ al	L-3-Cyclopentylalanine
5	Nle	L-Norleucine
	2-Nal	L-2-Naphthylalanine
	1-Nal	L-1-Naphthylalanine
	4Cl-Phe	L-4-Chlorophenylalanine
	3Cl-Phe	L-3-Chlorophenylalanine
10	2Cl-Phe	L-2-Chlorophenylalanine
	3,4Cl ₂ -Phe	L-3,4-Dichlorophenylalanine
	4F-Phe	L-4-Fluorophenylalanine
	3F-Phe	L-3-Fluorophenylalanine
	2F-Phe	L-2-Fluorophenylalanine
15	Tic	L-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid
	Thi	L-β-2-Thienylalanine
	Tza	L-2-Thiazolylalanine
	Mso	L-Methionine sulfoxide
	AcLys	L-N-Acetyllysine
20	Dpr	L-2,3-Diaminopropionic acid
	A ₂ Bu	L-2,4-Diaminobutyric acid
	Dbu	(S)-2,3-Diaminobutyric acid
	Abu	γ-Aminobutyric acid (GABA)
	Aha	ε-Aminohexanoic acid
25	Aib	α-Aminoisobutyric acid
	Y(Bzl)	L-O-Benzyltyrosine
	Bip	L-Biphenylalanine
	S(Bzl)	L-O-Benzylserine
	T(Bzl)	L-O-Benzylthreonine
30	hCha	L-Homo-cyclohexylalanine
	hCys	L-Homo-cysteine
	hSer	L-Homo-serine
	hArg	L-Homo-arginine
	hPhe	L-Homo-phenylalanine
35	Bpa	L-4-Benzoylphenylalanine
	Pip	L-Pipecolic acid

	OctG	L-Octylglycine
	MePhe	L-N-Methylphenylalanine
	MeNle	L-N-Methylnorleucine
	MeAla	L-N-Methylalanine
5	MeIle	L-N-Methylisoleucine
	MeVal	L-N-Methvaline
	MeLeu	L-N-Methylleucine

In addition, the most preferred values for B also include groups of type A8'' of (L)-
10 configuration:



A8''

wherein R²⁰ is H or lower alkyl and R⁶⁴ is alkyl; alkenyl; aryl; aryl-lower alkyl; or heteroaryl-
15 lower alkyl; especially those wherein R⁶⁴ is n-hexyl (A8''-21); n-heptyl (A8''-22); 4-(phenyl)benzyl (A8''-23); diphenylmethyl (A8''-24); 3-amino-propyl (A8''-25); 5-amino-pentyl (A8''-26); methyl (A8''-27); ethyl (A8''-28); isopropyl (A8''-29); isobutyl (A8''-30); n-propyl (A8''-31); cyclohexyl (A8''-32); cyclohexylmethyl (A8''-33); n-butyl (A8''-34); phenyl (A8''-35); benzyl (A8''-36); (3-indolyl)methyl (A8''-37); 2-(3-indolyl)ethyl (A8''-38);
20 (4-phenyl)phenyl (A8''-39); and n-nonyl (A8''-40).

The peptidic chains Z, Z¹ and Z² of the β -hairpin mimetics described herein are generally defined in terms of amino acid residues belonging to one of the following groups:

- **Group C** -NR²⁰CH(R⁷²)CO-; "hydrophobic: small to medium-sized"
- 25 - **Group D** -NR²⁰CH(R⁷³)CO-; "hydrophobic: large aromatic or heteroaromatic"
- **Group E** -NR²⁰CH(R⁷⁴)CO-; "polar-cationic", "acylamino" and "urea-derived"
- **Group F** -NR²⁰CH(R⁸⁴)CO-; "polar-non-charged"
- **Group H** -NR²⁰-CH(CO-)-(CH₂)₄₋₇-CH(CO-)-NR²⁰-;
-NR²⁰-CH(CO-)-(CH₂)_pSS(CH₂)_p-CH(CO-)-NR²⁰-;
30 -NR²⁰-CH(CO-)-(-(CH₂)_p)NR²⁰CO(CH₂)_p-CH(CO-)-NR²⁰-; and
-NR²⁰-CH(CO-)-(-(CH₂)_p)NR²⁰CONR²⁰(CH₂)_p-CH(CO-)-NR²⁰-;
"interstrand linkage"

Furthermore, the amino acid residues in chains Z, Z¹ and Z² can also be of formula -A-CO- or of formula -B-CO- wherein A and B are as defined above. Finally, Gly can also be an amino

acid residue in chains Z, Z¹ and Z², and Pro can be an amino acid residue in chains Z, Z¹ and Z², too, with the exception of positions where interstrand linkages (H) are possible.

5 **Group C** comprises amino acid residues with small to medium-sized *hydrophobic* side chain groups according to the general definition for substituent R⁷². A hydrophobic residue refers to an amino acid side chain that is uncharged at physiological pH and that is repelled by aqueous solution. Furthermore these side chains generally do *not* contain hydrogen bond donor groups, such as (but not limited to) primary and secondary amides, primary and secondary amines and the corresponding protonated salts thereof, thiols, alcohols, phosphonates, 10 phosphates, ureas or thioureas. However, they may contain hydrogen bond acceptor groups such as ethers, thioethers, esters, tertiary amides, alkyl- or aryl phosphonates and phosphates or tertiary amines. Genetically encoded small-to-medium-sized amino acids include alanine, isoleucine, leucine, methionine and valine.

15 **Group D** comprises amino acid residues with *aromatic* and *heteroaromatic* side chain groups according to the general definition for substituent R⁷³. An aromatic amino acid residue refers to a hydrophobic amino acid having a side chain containing at least one ring having a conjugated π -electron system (aromatic group). In addition they may contain hydrogen bond donor groups such as (but not limited to) primary and secondary amides, primary and 20 secondary amines and the corresponding protonated salts thereof, thiols, alcohols, phosphonates, phosphates, ureas or thioureas, and hydrogen bond acceptor groups such as (but not limited to) ethers, thioethers, esters, tertiary amides, alkyl- or aryl phosphonates -and phosphates or tertiary amines. Genetically encoded aromatic amino acids include phenylalanine and tyrosine.

25

A heteroaromatic amino acid residue refers to a hydrophobic amino acid having a side chain containing at least one ring having a conjugated π -system incorporating at least one heteroatom such as (but not limited to) O, S and N according to the general definition for substituent R⁷⁷. In addition such residues may contain hydrogen bond donor groups such as 30 (but not limited to) primary and secondary amides, primary and secondary amines and the corresponding protonated salts thereof, thiols, alcohols, phosphonates, phosphates, ureas or thioureas, and hydrogen bond acceptor groups such as (but not limited to) ethers, thioethers, esters, tertiary amides, alkyl- or aryl phosphonates -and phosphates or tertiary amines. Genetically encoded heteroaromatic amino acids include tryptophan and histidine.

35

Group E comprises amino acids containing side chains with polar-cationic, acylamino- and urea-derived residues according to the general definition for substituent R⁷⁴. Polar-cationic refers to a basic side chain which is protonated at physiological pH. Genetically encoded polar-cationic amino acids include arginine, lysine and histidine. Citrulline is an example for an urea derived amino acid residue.

Group F comprises amino acids containing side chains with polar-non-charged residues according to the general definition for substituent R⁸⁴. A polar-non-charged residue refers to a hydrophilic side chain that is uncharged at physiological pH, but that is not repelled by aqueous solutions. Such side chains typically contain hydrogen bond donor groups such as (but not limited to) primary and secondary amides, primary and secondary amines, thiols, alcohols, phosphonates, phosphates, ureas or thioureas. These groups can form hydrogen bond networks with water molecules. In addition they may also contain hydrogen bond acceptor groups such as (but not limited to) ethers, thioethers, esters, tertiary amides, alkyl- or aryl phosphonates and phosphates or tertiary amines. Genetically encoded polar-non-charged amino acids include asparagine, cysteine, glutamine, serine and threonine.

Group H comprises side chains of preferably (L)-amino acids at opposite positions of the β -strand region that can form an interstrand linkage. The most widely known linkage is the disulfide bridge formed by cysteines and homo-cysteines positioned at opposite positions of the β -strand. Various methods are known to form disulfide linkages including those described by: J. P. Tam et al. *Synthesis* 1979, 955-957; Stewart et al. , *Solid Phase Peptide Synthesis*, 2d Ed., Pierce Chemical Company, Ill., 1984; Ahmed et al. J. Biol. Chem. 1975, 250, 8477-8482 ; and Pennington et al., *Peptides*, pages 164-166, Giralt and Andreu, Eds., ESCOM Leiden, The Netherlands, 1990. Most advantageously, for the scope of the present invention, disulfide linkages can be prepared as described hereinafter in the pertinent Examples (procedure 3), using acetamidomethyl (Acm)- protective groups for cysteine. A well established interstrand linkage consists in linking ornithines and lysines, respectively, with glutamic and aspartic acid residues located at opposite β -strand positions by means of an amide bond formation. Preferred protective groups for the side chain amino-groups of ornithine and lysine are allyloxycarbonyl (Alloc) and allylesters for aspartic and glutamic acid as described hereinafter in the pertinent Examples (procedure 4). Finally, interstrand linkages can also be established by linking the amino groups of lysine and ornithine located at opposite β -strand positions with reagents such as N,N-carbonylimidazole to form cyclic ureas.

As mentioned earlier, positions for interstrand linkages are the following:

- If n=8: Positions P2 and P7 taken together;
 - if n=9: Positions P2 and P8 taken together;
 - if n=10: Positions P3 and P8 taken together;
 - if n=11: Positions P4 and P8; and/or P2 and P10 taken together;
 - 5 - if n=12: Positions P4 and P9; and/or P2 and P11 taken together;
 - if n=13: Positions P4 and P10; and/or Positions P2 and P12 taken together;
 - if n=14: Positions P5 and P10; and/or P3 and P12 taken together; and
 - if n=15: Positions P6 and P10; and/or P4 and P12; and/or P2 and P14.
 - if n=16: Positions P6 and P11; and/or P4 and P13; and/or P2 and P15 taken together.
- 10 Such interstrand linkages are known to stabilize the β -hairpin conformations and thus constitute an important structural element for the design of β -hairpin mimetics.

Most preferred amino acid residues chains Z, Z¹ and Z² are those derived from natural α -amino acids. Hereinafter follows a list of amino acids which, or the residues of which, are

15 suitable for the purposes of the present invention, the abbreviations corresponding to generally adopted usual practice:

	three letter code		one letter code
	Ala	L-Alanine	A
20	Arg	L-Arginine	R
	Asn	L-Asparagine	N
	Asp	L-Aspartic acid	D
	Cys	L-Cysteine	C
	Glu	L-Glutamic acid	E
25	Gln	L-Glutamine	Q
	Gly	Glycine	G
	His	L-Histidine	H
	Ile	L-Isoleucine	I
	Leu	L-Leucine	L
30	Lys	L-Lysine	K
	Met	L-Methionine	M
	Phe	L-Phenylalanine	F
	Pro	L-Proline	P
	^D Pro	D-Proline	^D P
35	Ser	L-Serine	S
	Thr	L-Threonine	T

Trp	L-Tryptophan	W
Tyr	L-Tyrosine	Y
Val	L-Valine	V

- 5 Other α -amino acids which, or the residues of which, are suitable for the purposes of the present invention include:

	Cit	L-Citrulline
	Orn	L-Ornithine
	tBuA	L-t-Butylalanine
10	Sar	Sarcosine
	Pen	L-Penicillamine
	t-BuG	L-tert.-Butylglycine
	4AmPhe	L-para-Aminophenylalanine
	3AmPhe	L-meta-Aminophenylalanine
15	2AmPhe	L-ortho-Aminophenylalanine
	Phe(mC(NH ₂)=NH)	L-meta-Amidinophenylalanine
	Phe(pC(NH ₂)=NH)	L-para-Amidinophenylalanine
	Phe(mNHC (NH ₂)=NH)	L-meta-Guanidinophenylalanine
	Phe(pNHC (NH ₂)=NH)	L-para-Guanidinophenylalanine
20	Phg	L-Phenylglycine
	Cha	L-Cyclohexylalanine
	C ₄ al	L-3-Cyclobutylalanine
	C ₃ al	L-3-Cyclopentylalanine
	Nle	L-Norleucine
25	2-Nal	L-2-Naphthylalanine
	1-Nal	L-1-Naphthylalanine
	4Cl-Phe	L-4-Chlorophenylalanine
	3Cl-Phe	L-3-Chlorophenylalanine
	2Cl-Phe	L-2-Chlorophenylalanine
30	3,4Cl ₂ -Phe	L-3,4-Dichlorophenylalanine
	4F-Phe	L-4-Fluorophenylalanine
	3F-Phe	L-3-Fluorophenylalanine
	2F-Phe	L-2-Fluorophenylalanine
	Tic	1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid
35	Thi	L- β -2-Thienylalanine
	Tza	L-2-Thiazolylalanine

	Mso	L-Methionine sulfoxide
	AcLys	N-Acetyllysine
	Dpr	2,3-Diaminopropionic acid
	A ₂ Bu	2,4-Diaminobutyric acid
5	Dbu	(S)-2,3-Diaminobutyric acid
	Abu	γ-Aminobutyric acid (GABA)
	Aha	ε-Aminohexanoic acid
	Aib	α-Aminoisobutyric acid
	Y(Bzl)	L-O-Benzyltyrosine
10	Bip	L-(4-phenyl)phenylalanine
	S(Bzl)	L-O-Benzylserine
	T(Bzl)	L-O-Benzylthreonine
	hCha	L-Homo-cyclohexylalanine
	hCys	L-Homo-cysteine
15	hSer	L-Homo-serine
	hArg	L-Homo-arginine
	hPhe	L-Homo-phenylalanine
	Bpa	L-4-Benzoylphenylalanine
	4-AmPyr1	(2S,4S)-4-Amino-pyrrolidine-L-carboxylic acid
20	4-AmPyr2	(2S,4R)-4-Amino-pyrrolidine-L-carboxylic acid
	4-PhePyr1	(2S,5R)-4-Phenyl-pyrrolidine-L-carboxylic acid
	4-PhePyr2	(2S,5S)-4-Phenyl-pyrrolidine-L-carboxylic acid
	5-PhePyr1	(2S,5R)-5-Phenyl-pyrrolidine-L-carboxylic acid
	5-PhePyr2	(2S,5S)-5-Phenyl-pyrrolidine-L-carboxylic acid
25	Pro(4-OH)1	(4S)-L-Hydroxyproline
	Pro(4-OH)2	(4R)-L-Hydroxyproline
	Pip	L-Pipecolic acid
	^D Pip	D-Pipecolic acid
	OctG	L-Octylglycine
30	MePhe	L-N-Methylphenylalanine
	MeNle	L-N-Methylnorleucine
	MeAla	L-N-Methylalanine
	MeIle	L-N-Methylisoleucine
	MeVal	L-N-Methylvaline
35	MeLeu	L-N-Methylleucine

Particularly preferred residues for **group C** are:

	Ala	L-Alanine
	Ile	L-Isoleucine
	Leu	L-Leucine
5	Met	L-Methionine
	Val	L-Valine
	tBuA	L-t-Butylalanine
	t-BuG	L-tert.-Butylglycine
	Cha	L-Cyclohexylalanine
10	C ₄ al	L-3-Cyclobutylalanine
	C ₅ al	L-3-Cyclopentylalanine
	Nle	L-Norleucine
	hCha	L-Homo-cyclohexylalanine
	OctG	L-Octylglycine
15	MePhe	L-N-Methylphenylalanine
	MeNle	L-N-Methylnorleucine
	MeAla	L-N-Methylalanine
	MeIle	L-N-Methylisoleucine
	MeVal	L-N-Methylvaline
20	MeLeu	L-N-Methylleucine

Particularly preferred residues for **group D** are:

	His	L-Histidine
	Phe	L-Phenylalanine
25	Trp	L-Tryptophan
	Tyr	L-Tyrosine
	Phg	L-Phenylglycine
	2-Nal	L-2-Naphthylalanine
	1-Nal	L-1-Naphthylalanine
30	4Cl-Phe	L-4-Chlorophenylalanine
	3Cl-Phe	L-3-Chlorophenylalanine
	2Cl-Phe	L-2-Chlorophenylalanine
	3,4Cl ₂ -Phe	L-3,4-Dichlorophenylalanine
	4F-Phe	L-4-Fluorophenylalanine
35	3F-Phe	L-3-Fluorophenylalanine
	2F-Phe	L-2-Fluorophenylalanine
	Thi	L-β-2-Thienylalanine

	Tza	L-2-Thiazolylalanine
	Y(Bzl)	L-O-Benzyltyrosine
	Bip	L-Biphenylalanine
	S(Bzl)	L-O-Benzylserine
5	T(Bzl)	L-O-Benzylthreonine
	hPhe	L-Homo-phenylalanine
	Bpa	L-4-Benzoylphenylalanine

Particularly preferred residues for **group E** are

10	Arg	L-Arginine
	Lys	L-Lysine
	Orn	L-Ornithine
	Dpr	L-2,3-Diaminopropionic acid
	A ₂ Bu	L-2,4-Diaminobutyric acid
15	Dbu	(S)-2,3-Diaminobutyric acid
	Phe(pNH ₂)	L-para-Aminophenylalanine
	Phe(mNH ₂)	L-meta-Aminophenylalanine
	Phe(oNH ₂)	L-ortho-Aminophenylalanine
	hArg	L-Homo-arginine
20	Phe(mC(NH ₂)=NH)	L-meta-Amidinophenylalanine
	Phe(pC(NH ₂)=NH)	L-para-Amidinophenylalanine
	Phe(mNHC(NH ₂)=NH)	L-meta-Guanidinophenylalanine
	Phe(pNHC(NH ₂)=NH)	L-para-Guanidinophenylalanine
	Cit	L-Citrulline

25

Particularly preferred residues for **group F** are

	Asn	L-Asparagine
	Cys	L-Cysteine
30	Glu	L-Glutamine
	Ser	L-Serine
	Thr	L-Threonine
	Cit	L-Citrulline
	Pen	L-Penicillamine
35	AcLys	L-N ^ε -Acetyllysine
	hCys	L-Homo-cysteine
	hSer	L-Homo-serine

In the dimeric structures **Ib** the preferred substituents forming groups G1 and G2 are the following, with the proviso that R³³ is lower alkyl; or lower alkenyl; R³⁴ is H; or lower alkyl; and R⁶¹ is H:

- 5 R²: -(CH₂)_mO-; -(CH₂)_mNR³³R³⁴-; -(CH₂)_oCO-
 R⁵: -(CH₂)_oO-; -(CH₂)_oNR³³R³⁴-; -(CH₂)_oCO-
 R⁶: -(CH₂)_oO-; -(CH₂)_oNR³³R³⁴-; -(CH₂)_oCO-
 R⁸: -(CH₂)_oO-; -(CH₂)_oNR³³R³⁴-; -(CH₂)_oCO-
 R⁹: -(CH₂)_oO-; -(CH₂)_oNR³³R³⁴-; -(CH₂)_oCO-
 10 R¹⁰: -(CH₂)_oO-; -(CH₂)_oNR³³R³⁴-; -(CH₂)_oCO-
 R¹¹: -(CH₂)_mO-; -(CH₂)_mNR³³R³⁴-; -(CH₂)_oCO-
 R¹⁴: -(CH₂)_mO-; -(CH₂)_mNR³³R³⁴-; -(CH₂)_oCO-
 R¹⁵: -(CH₂)_mO-; -(CH₂)_mNR³³R³⁴-; -(CH₂)_oCO-
 R¹⁶: -(CH₂)_mO-; -(CH₂)_mNR³³R³⁴-; -(CH₂)_oCO-
 15 R¹⁸: -(CH₂)_pO-; -(CH₂)_pNR³³R³⁴-; -(CH₂)_pCO-
 R¹⁹: -(CH₂)_pO-; -(CH₂)_pNR³³R³⁴-; -(CH₂)_pCO-
 R²¹: -(CH₂)_oO-; -(CH₂)_oNR³³R³⁴-; -(CH₂)_oCO-
 R²³: -(CH₂)_oO-; -(CH₂)_oNR³³R³⁴-; -(CH₂)_oCO-
 R²⁴: -(CH₂)_oO-; -(CH₂)_oNR³³R³⁴-; -(CH₂)_oCO-
 20 R²⁵: -(CH₂)_mO-; -(CH₂)_mNR³³R³⁴-; -(CH₂)_oCO-
 R²⁶: -(CH₂)_mO-; -(CH₂)_mNR³³R³⁴-; -(CH₂)_oCO-
 R²⁸: -(CH₂)_oO-; -(CH₂)_oNR³³R³⁴-; -(CH₂)_oCO-
 R²⁹: -(CH₂)_oO-; -(CH₂)_oNR³³R³⁴-; -(CH₂)_oCO-
 R³¹: -(CH₂)_pO-; -(CH₂)_pNR³³R³⁴-; -(CH₂)_pCO-
 25 R³⁷: -(CH₂)_pO-; -(CH₂)_pNR³³R³⁴-; -(CH₂)_oCO-
 R³⁸: -(CH₂)_pO-; -(CH₂)_pNR³³R³⁴-; -(CH₂)_oCO-
 R⁴¹: -(CH₂)_pO-; -(CH₂)_pNR³³R³⁴-; -(CH₂)_oCO-
 R⁴²: -(CH₂)_pO-; -(CH₂)_pNR³³R³⁴-; -(CH₂)_oCO-
 R⁴⁵: -(CH₂)_oO-; -(CH₂)_oNR³³R³⁴-; -(CH₂)_sCO-
 30 R⁴⁷: -(CH₂)_oO-
 R⁴⁹: -(CH₂)_sO-; -(CH₂)_sCO-
 R⁵¹: -(CH₂)_mO-; -(CH₂)_mNR³³R³⁴-; -(CH₂)_oCO-
 R⁵²: -(CH₂)_mO-; -(CH₂)_mNR³³R³⁴-; -(CH₂)_oCO-
 R⁵³: -(CH₂)_mO-; -(CH₂)_mNR³³R³⁴-; -(CH₂)_oCO-

- 35 and with the further provisos that the preferred linker molecules **L** are as defined below, that
 R³⁴ is H; or lower alkyl; X is O; S; NR³⁴; -NR³⁴CONR³⁴; or -OCOO-; and Y is
 C₆R⁶⁷R⁶⁸R⁶⁹R⁷⁰:

- L1: $-(CH_2)_p [X(CH_2)_p]_o-$
 L2: $-CO(CH_2)_p [X(CH_2)_p]_o CO-$
 L3: $-CONR^{34}(CH_2)_p [X(CH_2)_p]_o NR^{34}CO-$
 L4: $-O(CH_2)_p [X(CH_2)_p]_o O-$
 5 L6: $-NR^{34}(CH_2)_p [X(CH_2)_p]_o NR^{34}-$
 L7: $-(CH_2)_o Y(CH_2)_o-$
 L8: $-CO(CH_2)_o Y(CH_2)_o CO-$
 L9: $-CONR^{34}(CH_2)_o Y(CH_2)_o NR^{34}CO-$
 L10: $-O(CH_2)_o Y(CH_2)_o O-$
 10 L11: $-S(CH_2)_o Y(CH_2)_o S-$
 L12: $-NR^{34}(CH_2)_o Y(CH_2)_o NR^{34}-$
 L13: $-CO(CH_2)_p [X(CH_2)_p]_o NR^{34}-$
 L14: $-CO(CH_2)_o Y(CH_2)_o NR^{34}-$
 L15: $-NR^{34}(CH_2)_p [X(CH_2)_p]_o CO-$
 15 L16: $-NR^{34}(CH_2)_o Y(CH_2)_o CO-$

with the proviso that

- $-(CH_2)_m O-$ can be combined with linker L1, L2, L3, L7, L8 or L9;
 $-(CH_2)_o O-$ can be combined with linker L1, L2, L3, L7, L8 or L9;
 $-(CH_2)_p O-$ can be combined with linker L1, L2, L3, L7, L8 or L9;
 20 $-(CH_2)_s O-$ can be combined with linker L1, L2, L3, L7, L8 or L9;
 $-(CH_2)_m NR^{34}-$ can be combined with linker L1, L2, L3, L7, L8 or L9;
 $-(CH_2)_o NR^{34}-$ can be combined with linker L1, L2, L3, L7, L8 or L9;
 $-(CH_2)_p NR^{34}-$ can be combined with linker L1, L2, L3, L7, L8 or L9;
 $-(CH_2)_o CO-$ can be combined with linker L4, L5, L6, L10, L11 or L12;
 25 $-(CH_2)_p CO-$ can be combined with linker L4, L5, L6, L10, L11 or L12;
 $-(CH_2)_s CO-$ can be combined with linker L4, L5, L6, L10, L11 or L12;
 $-(CH_2)_m O-$ can be combined with linker L13 or L14 and the resulting combination with
 $-(CH_2)_o CO-$; $-(CH_2)_p CO-$; or $-(CH_2)_s CO-$;
 $-(CH_2)_o O-$ can be combined with linker L13 or L14 and the resulting combination with
 30 $-(CH_2)_o CO-$; $-(CH_2)_p CO-$; or $-(CH_2)_s CO-$;
 $-(CH_2)_p O-$ can be combined with linker L13 or L14 and the resulting combination with
 $-(CH_2)_o CO-$; $-(CH_2)_p CO-$; or $-(CH_2)_s CO-$;
 $-(CH_2)_s O-$ can be combined with linker L13 or L14 and the resulting combination with
 $-(CH_2)_o CO-$; $-(CH_2)_p CO-$; or $-(CH_2)_s CO-$;
 35 $-(CH_2)_m NR^{34}-$ can be combined with linker L13 or L14 and the resulting combination with
 $-(CH_2)_o CO-$; $-(CH_2)_p CO-$; or $-(CH_2)_s CO-$;
 $-(CH_2)_o NR^{34}-$ can be combined with linker L13 or L14 and the resulting combination with

- $-(CH_2)_oCO-$; $-(CH_2)_pCO-$; or $-(CH_2)_sCO-$;
 $-(CH_2)_pNR^{34}-$ can be combined with linker L13 or L14 and the resulting combination with
 $-(CH_2)_oCO-$; $-(CH_2)_pCO-$; or $-(CH_2)_sCO-$;
 $-(CH_2)_oCO-$ can be combined with linker L15 or L16 and the resulting combination with
5 $-(CH_2)_mX-$; $-(CH_2)_oX-$; $-(CH_2)_pX-$; or $-(CH_2)_qX-$;
 $-(CH_2)_pCO-$ can be combined with linker L15 or L16 and the resulting combination with
 $-(CH_2)_mX-$; $-(CH_2)_oX-$; $-(CH_2)_pX-$; or $-(CH_2)_qX-$;
 $-(CH_2)_sCO-$ can be combined with linker L15 or L16 and the resulting combination with
 $-(CH_2)_mX-$; $-(CH_2)_oX-$; $-(CH_2)_pX-$; or $-(CH_2)_qX-$.

10

Generally, the peptidic chain Z, Z¹ or Z² within the β -hairpin mimetics of the invention comprises 8-16 amino acid residues ($n = 8-16$). The positions P¹ to Pⁿ of each amino acid residue in the chain Z, Z¹ or Z² are unequivocally defined as follows: P¹ represents the first amino acid in the chain Z, Z¹ or Z² that is coupled with its N-terminus to the C-terminus of
 15 the templates (b)-(p) or of group -B-CO- in template (a1), or of group -A-CO- in template a2, and Pⁿ represents the last amino acid in the chain Z, Z¹ or Z² that is coupled with its C-terminus to the N-terminus of the templates (b)-(p) or of group -A-CO- in template (a1) or of group -B-CO- in template (a2). Each of the positions P¹ to Pⁿ will preferably contain an amino acid residue belonging to one or two of above types C to F, as follows:

20 - If n is 8, the amino acid residues in position 1 – 8 are preferably:

- P1: of type C or of type D; or of type E;
- P2: of type E; or of type D;
- P3: of type E;
- P4: of type E or of formula -A1-A69-CO-;
- 25 - P5: of type E or of formula -B-CO-;
- P6: of type D;
- P7: of type E; or of type D and
- P8: of type C or of type D; or of type E;
- at P4 and P5 also D-isomers being possible;

30 - if n is 9, the amino acid residues in position 1 – 9 are preferably:

- P1: of type C or of type D; or of type E;
- P2: of type E; or of type D;
- P3: of type C;
- P4: of type E, or the residue is Pro;
- 35 - P5: of type E, or the residue is Pro;
- P6: of type D or of type E, or the residue is Pro;
- P7: of type E or of type D;

- P8: of type E; or of type D and
- P9: of type C or of type D; or of type E;
- at P4, P5 and P6 also D-isomers being possible;
- if n is 10, the amino acid residues in position 1 – 10 are preferably:
 - 5 - P1: of type C or of type D; or of type E;
 - P2: of type E; or of type D;
 - P3: of type C;
 - P4: of type E or of type D;
 - P5: of type E or of formula -A1-A69-CO-;
 - 10 - P6: of type E or of formula -B-CO-;
 - P7: of type D or of type E;
 - P8: of type D;
 - P9: of type E; or of type D and
 - P10: of type C or of type D; or of type E;
 - 15 - at P5 and P6 also D-isomers being possible;
- if n is 11, the amino acid residues in position 1 – 11 are preferably:
 - P1: of type C or of type D; or of type E;
 - P2: of type E; or of type D;
 - P3: of type D;
 - 20 - P4: of type E or of type C;
 - P5: of type E, or the residue is Pro;
 - P6: of type E, or the residue is Pro;
 - P7: of type E, or the residue is Pro;
 - P8: of type D or of type E;
 - 25 - P9: of type D;
 - P10: of type E; or of type D and
 - P11: of type C or of type D; or of type E;
 - at P5, P6 and P7 also D-isomers being possible;
- if n is 12, the amino acid residues in position 1 – 12 are preferably:
 - 30 - P1: of type C or of type E; or of type D; or of type F;
 - P2: of type E; or of type D;
 - P3: of type C or of type D;
 - P4: of type E;
 - P5: of type E; or of type C;
 - 35 - P6: of type E or of type F or of formula -A1-A69-CO-;
 - P7: of type E or of formula -B-CO-;
 - P8: of type D;

- P9: of type E or of type D;
- P10: of type D;
- P11: of type E; or of type D and
- P12: of type C or of type E; or of type D; or of type F;
- 5 - at P6 and P7 also D-isomers being possible;
- if n is 13, the amino acid residues in position 1 – 13 are preferably:
 - P1: of type C or of type D; or of type E;
 - P2: of type E; or of type D;
 - P3: of type C or of type D;
 - 10 - P4: of type E or of type C;
 - P5: of type E or of type D;
 - P6: of type E or of type F, or the residue is Pro;
 - P7: of type E, or the residue is Pro;
 - P8: of type D, or the residue is Pro;
 - 15 - P9: of type D;
 - P10: of type E or of type C;
 - P11: of type C or of type D;
 - P12: of type E; or of type D and
 - P13: of type C or of type D; or of type E;
 - 20 - at P6, P7 and P8 also D-isomers being possible;
 - if n is 14, the amino acid residues in position 1 – 14 are preferably:
 - P1: of type C or of type D; or of type E;
 - P2: of type E; or of type D;
 - P3: of type C or of type D;
 - 25 - P4: of type D;
 - P5: of type E;
 - P6: of type E;
 - P7: of type E or of type F or of formula -A1-A69-CO-;
 - P8: of type E or of formula -B-CO-;
 - 30 - P9: of type D;
 - P10: of type C;
 - P11: of type E or of type D;
 - P12: of type D or of type C;
 - P13: of type E; or of type D and
 - 35 - P14: of type C or of type D; or of type E;
 - at P7 and P8 also D-isomers being possible;
 - if n is 15, the amino acid residues in position 1 – 15 are preferably:

- P1: of type C and of type D; or of type E;
- P2: of type E; or of type D;
- P3: of type C and of type D;
- P4: of type E or of type C;
- 5 - P5: of type C;
- P6: of type E or of type D;
- P7: of type C, or the residue is Pro;
- P8: of type E or of type F, or the residue is Pro;
- P9: of type E or of type F, or the residue is Pro;
- 10 - P10: of type E;
- P11: of type C;
- P12: of type E or of type C;
- P13: of type D or of type C;
- P14: of type E; or of type D and
- 15 - P15: of type C and of type D; or of type E;
- at P7, P8 and P9 also D-isomers being possible; and
- if n is 16, the amino acid residues in position 1 – 16 are preferably:
 - P1: of type D; or of type E;
 - P2: of type E; or of type D;
 - 20 - P3: of type C or of type D;
 - P4: of type E or of type D;
 - P5: of type D;
 - P6: of type E;
 - P7: of type E or of type F;
 - 25 - P8: of type E or of type F or of formula -A1-A69-CO-;
 - P9: of type E or of formula -B-CO-;
 - P10: of type D;
 - P11: of type E;
 - P12: of type D;
 - 30 - P13: of type E or of type C;
 - P14: of type C or of type D;
 - P15: of type E; or of type D and
 - P16: of type C or of type D; or of type E;
 - at P8 and P9 also D-isomers being possible.
- 35

If n is 12, the amino acid residues in position 1 – 12 are most preferably:

- P1: Leu; Arg; Lys; Tyr; Trp; Val; Gln; or 4-AmPhe;

- P2: Arg; Trp; or Gln;
- P3: Leu; Val; Ile; or Phe;
- P4: Lys; Arg; Gln; or Orn;
- P5: Lys; or Arg;
- 5 - P6: Arg; Y(Bzl); or ^DY(Bzl);
- P7: Arg;
- P8: Trp; Bip; 1-Nal; Y(Bzl); or Val;
- P9: Lys; Arg; Orn; Tyr; Trp; or Gln;
- P10: Tyr; T(Bzl); or Y(Bzl);
- 10 - P11: Arg; or Tyr; and
- P12: Val; Arg; 1-Nal; or 4-AmPhe.

Particularly preferred β -peptidomimetics of the invention include those described in Examples 106, 137, 161, 197, 206, 222, 230, 250, 256, 267, 277, 281, 283, 284, 285, 286,
15 289, 294, 295, 296, 297, and 298.

The process of the invention can advantageously be carried out as parallel array synthesis to yield libraries of template-fixed β -hairpin peptidomimetics of the above general formula I. Such parallel synthesis allows one to obtain arrays of numerous (normally 24 to 192, typically 96) compounds of general formula I in high yields and defined purities, minimizing the
20 formation of dimeric and polymeric by-products. The proper choice of the functionalized solid-support (i.e. solid support plus linker molecule), templates and site of cyclization play thereby key roles.

The functionalized solid support is conveniently derived from polystyrene crosslinked with, preferably 1-5%, divinylbenzene; polystyrene coated with polyethyleneglycol spacers (Tentagel^R); and polyacrylamide resins (see also Obrecht, D.; Villalgordo, J.-M, "Solid-Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compound Libraries", *Tetrahedron Organic Chemistry Series*, Vol. 17, Pergamon, Elsevier Science, 1998).
25

30 The solid support is functionalized by means of a linker, i.e. a bifunctional spacer molecule which contains on one end an anchoring group for attachment to the solid support and on the other end a selectively cleavable functional group used for the subsequent chemical transformations and cleavage procedures. For the purposes of the present invention the linker
35 must be designed to eventually release the carboxyl group under mild acidic conditions which do not affect protecting groups present on any functional group in the side-chains of the

various amino acids. Linkers which are suitable for the purposes of the present invention form acid-labile esters with the carboxyl group of the amino acids, usually acid-labile benzyl, benzhydryl and trityl esters; examples of linker structures of this kind include 2-methoxy-4-hydroxymethylphenoxy (Sasrin^R linker), 4-(2,4-dimethoxyphenyl-hydroxymethyl)-phenoxy (Rink linker), 4-(4-hydroxymethyl-3-methoxyphenoxy)butyric acid (HMPB linker), trityl and 2-chlorotrityl.

Preferably, the support is derived from polystyrene crosslinked with, most preferably 1-5%, divinylbenzene and functionalized by means of the 2-chlorotrityl linker.

10

When carried out as a parallel array synthesis the process of the invention can be advantageously carried out as described hereinbelow but it will be immediately apparent to those skilled in the art how this procedure will have to be modified in case it is desired to synthesize one single compound of the above formula Ia or Ib.

15

A number of reaction vessels (normally 24 to 192, typically 96) equal to the total number of compounds to be synthesized by the parallel method are loaded with 25 to 1000 mg, preferably 100 mg, of the appropriate functionalized solid support, preferably 1 to 3% cross linked polystyrene or tentagel resin.

20

The solvent to be used must be capable of swelling the resin and includes, but is not limited to, dichloromethane (DCM), dimethylformamide (DMF), N-methylpyrrolidone (NMP), dioxane, toluene, tetrahydrofuran (THF), ethanol (EtOH), trifluoroethanol (TFE), isopropylalcohol and the like. Solvent mixtures containing as at least one component a polar solvent (e. g. 20% TFE/DCM, 35% THF/NMP) are beneficial for ensuring high reactivity and solvation of the resin-bound peptide chains (Fields, G. B., Fields, C. G., *J. Am. Chem. Soc.* 1991, 113, 4202-4207).

25

With the development of various linkers that release the C-terminal carboxylic acid group under mild acidic conditions, not affecting acid-labile groups protecting functional groups in the side chain(s), considerable progresses have been made in the synthesis of protected peptide fragments. The 2-methoxy-4-hydroxybenzylalcohol-derived linker (Sasrin^R linker, Mergler et al., *Tetrahedron Lett.* 1988, 29 4005-4008) is cleavable with diluted trifluoroacetic acid (0.5-1% TFA in DCM) and is stable to Fmoc deprotection conditions during the peptide synthesis, Boc/tBu-based additional protecting groups being compatible with this protection scheme. Other linkers which are suitable for the process of the invention include the super acid labile 4-(2,4-dimethoxyphenyl-hydroxymethyl)-phenoxy linker (Rink linker, Rink, H.

30

35

Tetrahedron Lett. 1987, 28, 3787-3790), where the removal of the peptide requires 10% acetic acid in DCM or 0.2% trifluoroacetic acid in DCM; the 4-(4-hydroxymethyl-3-methoxyphenoxy)butyric acid-derived linker (HMPB-linker, Flörsheimer & Riniker, *Peptides* 1991, 1990 131) which is also cleaved with 1%TFA/DCM in order to yield a peptide fragment
 5 containing all acid labile side- chain protective groups; and, in addition, the 2-chlorotritylchloride linker (Barlos et al., *Tetrahedron Lett.* 1989, 30, 3943-3946), which allows the peptide detachment using a mixture of glacial acetic acid/trifluoroethanol/DCM (1:2:7) for 30 min.

10 Suitable protecting groups for amino acids and, respectively, for their residues are, for example,

- for the amino group (as is present e. g. also in the side-chain of lysine)

	Cbz	benzyloxycarbonyl
15	Boc	tert.-butyloxycarbonyl
	Fmoc	9-fluorenylmethoxycarbonyl
	Alloc	allyloxycarbonyl
	Teoc	trimethylsilylethoxycarbonyl
	Tcc	trichloroethoxycarbonyl
20	Nps	o-nitrophenylsulfonyl;
	Trt	triphenylmethyl or trityl

- for the carboxyl group (as is present e. g. also in the side-chain of aspartic and glutamic acid) by conversion into esters with the alcohol components

25

	tBu	tert.-butyl
	Bn	benzyl
	Me	methyl
	Ph	phenyl
30	Pac	Phenacyl
		Allyl
	Tse	trimethylsilylethyl
	Tce	trichloroethyl;

35 - for the guanidino group (as is present e. g. in the side-chain of arginine)

	Pmc	2,2,5,7,8-pentamethylchroman-6-sulfonyl
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Ts	tosyl (i. e. p-toluenesulfonyl)
Cbz	benzyloxycarbonyl
Pbf	pentamethyldihydrobenzofuran-5-sulfonyl

- 5 - for the hydroxy group (as is present e. g. in the side-chain of threonine and serine)

tBu	tert.-butyl
Bn	benzyl
Trt	trityl

10

- and for the mercapto group (as is present e. g. in the side-chain of cysteine)

Acm	acetamidomethyl
tBu	tert.-butyl
Bn	benzyl
Trt	trityl
Mtr	4-methoxytrityl.

15

The 9-fluorenylmethoxycarbonyl- (Fmoc)-protected amino acid derivatives are preferably used as the building blocks for the construction of the template-fixed β -hairpin loop mimetics of formulae Ia and Ib. For the deprotection, i. e. cleaving off of the Fmoc group, 20% piperidine in DMF or 2% DBU/2% piperidine in DMF can be used.

20

The quantity of the reactant, i. e. of the amino acid derivative, is usually 1 to 20 equivalents based on the milliequivalents per gram (meq/g) loading of the functionalized solid support (typically 0.1 to 2.85 meq/g for polystyrene resins) originally weighed into the reaction tube. Additional equivalents of reactants can be used if required to drive the reaction to completion in a reasonable time. The reaction tubes, in combination with the holder block and the manifold, are reinserted into the reservoir block and the apparatus is fastened together. Gas flow through the manifold is initiated to provide a controlled environment, for example, nitrogen, argon, air and the like. The gas flow may also be heated or chilled prior to flow through the manifold. Heating or cooling of the reaction wells is achieved by heating the reaction block or cooling externally with isopropanol/dry ice and the like to bring about the desired synthetic reactions. Agitation is achieved by shaking or magnetic stirring (within the reaction tube). The preferred workstations (without, however, being limited thereto) are

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35 Labsource's Combi-chem station and MultiSyn Tech's-Syro synthesizer.

Amide bond formation requires the activation of the α -carboxyl group for the acylation step. When this activation is being carried out by means of the commonly used carbodiimides such as dicyclohexylcarbodiimide (DCC, Sheehan & Hess, *J. Am. Chem. Soc.* 1955, 77, 1067-1068) or diisopropylcarbodiimide (DIC, Sarantakis et al *Biochem. Biophys. Res.*

- 5 *Commun.* 1976, 73, 336-342), the resulting dicyclohexylurea is insoluble and, respectively, diisopropylurea is soluble in the solvents generally used. In a variation of the carbodiimide method 1-hydroxybenzotriazole (HOBt, König & Geiger, *Chem. Ber* 1970, 103, 788-798) is included as an additive to the coupling mixture. HOBt prevents dehydration, suppresses racemization of the activated amino acids and acts as a catalyst to improve the sluggish
- 10 coupling reactions. Certain phosphonium reagents have been used as direct coupling reagents, such as benzotriazol-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP) (Castro et al., *Tetrahedron Lett.* 1975, 14, 1219-1222; *Synthesis*, 1976, 751-752), or benzotriazol-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (Py-BOP, Coste et al., *Tetrahedron Lett.* 1990, 31, 205-208), or 2-(1H-benzotriazol-1-yl)-1,1,3,3-
- 15 tetramethyluronium tetrafluoroborate (TBTU), or hexafluorophosphate (HBTU, Knorr et al., *Tetrahedron Lett.* 1989, 30, 1927-1930); these phosphonium reagents are also suitable for in situ formation of HOBt esters with the protected amino acid derivatives. More recently diphenoxyphosphoryl azide (DPPA) or O-(7-aza-benzotriazol-1-yl)-N,N,N',N'-
- 20 tetramethyluronium tetrafluoroborate (TATU) or O-(7-aza-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU)/7-aza-1-hydroxy benzotriazole (HOAt, Carpino et al., *Tetrahedron Lett.* 1994, 35, 2279-2281) have also been used as coupling reagents.

- Due to the fact that near-quantitative coupling reactions are essential it is desirable to have
- 25 experimental evidence for completion of the reactions. The ninhydrin test (Kaiser et al., *Anal. Biochemistry* 1970, 34, 595), where a positive colorimetric response to an aliquot of resin-bound peptide indicates qualitatively the presence of the primary amine, can easily and quickly be performed after each coupling step. Fmoc chemistry allows the spectrophotometric detection of the Fmoc chromophore when it is released with the base (Meienhofer et al., *Int. J.*
- 30 *Peptide Protein Res.* 1979, 13, 35-42).

The resin-bound intermediate within each reaction tube is washed free of excess of retained reagents, of solvents, and of by-products by repetitive exposure to pure solvent(s) by one of the two following methods:

35

- 1) The reaction wells are filled with solvent (preferably 5 ml), the reaction tubes, in combination with the holder block and manifold, are immersed and agitated for 5 to 300

minutes, preferably 15 minutes, and drained by gravity followed by gas pressure applied through the manifold inlet (while closing the outlet) to expel the solvent;

- 2) The manifold is removed from the holder block, aliquots of solvent (preferably 5 ml) are dispensed through the top of the reaction tubes and drained by gravity through a filter into a receiving vessel such as a test tube or vial.

Both of the above washing procedures are repeated up to about 50 times (preferably about 10 times), monitoring the efficiency of reagent, solvent, and byproduct removal by methods such as TLC, GC, or inspection of the washings.

The above described procedure of reacting the resin-bound compound with reagents within the reaction wells followed by removal of excess reagents, by-products, and solvents is repeated with each successive transformation until the final resin-bound fully protected linear peptide has been obtained.

Before this fully protected linear peptide is detached from the solid support, it is possible, if desired, to selectively deprotect one or several protected functional group(s) present in the molecule and to appropriately substitute the reactive group(s) thus liberated. To this effect, the functional group(s) in question must initially be protected by a protecting group which can be selectively removed without affecting the remaining protecting groups present. Alloc (allyloxycarbonyl) is an example for such a protecting group for amino which can be selectively removed, e.g. by means of Pd^0 and phenylsilane in CH_2Cl_2 , without affecting the remaining protecting groups, such as Fmoc, present in the molecule. The reactive group thus liberated can then be treated with an agent suitable for introducing the desired substituent. Thus, for example, an amino group can be acylated by means of an acylating agent corresponding to the acyl substituent to be introduced.

Detachment of the fully protected linear peptide from the solid support is achieved by immersion of the reaction tubes, in combination with the holder block and manifold, in reaction wells containing a solution of the cleavage reagent (preferably 3 to 5 ml). Gas flow, temperature control, agitation, and reaction monitoring are implemented as described above and as desired to effect the detachment reaction. The reaction tubes, in combination with the holder block and manifold, are disassembled from the reservoir block and raised above the solution level but below the upper lip of the reaction wells, and gas pressure is applied through the manifold inlet (while closing the outlet) to efficiently expel the final product solution into the reservoir wells. The resin remaining in the reaction tubes is then washed 2 to

5 times as above with 3 to 5 ml of an appropriate solvent to extract (wash out) as much of the detached product as possible. The product solutions thus obtained are combined, taking care to avoid cross-mixing. The individual solutions/extracts are then manipulated as needed to isolate the final compounds. Typical manipulations include, but are not limited to,
5 evaporation, concentration, liquid/liquid extraction, acidification, basification, neutralization or additional reactions in solution.

The solutions containing fully protected linear peptide derivatives which have been cleaved off from the solid support and neutralized with a base, are evaporated. Cyclization is then
10 effected in solution using solvents such as DCM, DMF, dioxane, THF and the like. Various coupling reagents which were mentioned earlier can be used for the cyclization. The duration of the cyclization is about 6-48 hours, preferably about 24 hours. The progress of the reaction is followed, e. g. by RP-HPLC (Reverse Phase High Performance Liquid Chromatography). Then the solvent is removed by evaporation, the fully protected cyclic peptide derivative is
15 dissolved in a solvent which is not miscible with water, such as DCM, and the solution is extracted with water or a mixture of water-miscible solvents, in order to remove any excess of the coupling reagent.

Before removing the protecting groups from the fully protected cyclic peptide, it is possible, if
20 desired, to form an interstrand linkage between side-chains of appropriate amino acid residues at opposite positions of the β -strand region; and/or to connect two building blocks of the type of formula Ia via a bridge -G1 - L - G2- to give a dimeric structure of the type of formula Ib.

Interstrand linkages and their formation have been discussed above, in connection with the
25 explanations made regarding groups of the type H which can, for example, be disulfide bridges formed by cysteines and homocysteines at opposite positions of the β -strand, or glutamic and aspartic acid residues linking ornithines and, respectively, lysines located at opposite β -strand positions by amide bond formation. The formation of such interstrand linkages can be effected by methods well known in the art.

30 Interstrand linkages and their formation have been discussed above, in connection with the explanations made regarding groups of the type H which can, for example, be disulfide bridges formed by cysteines and homocysteines at opposite positions of the β -strand, or glutamic and aspartic acid residues linking ornithines and, respectively, lysines located at
35 opposite β -strand positions by amide bond formation. The formation of such interstrand linkages can be effected by methods well known in the art.

For building up a bridge -G1 - L - G2- to give a dimeric structure, methods well known in the art can be used, too. Thus, for example, a fully side-chain protected β -hairpin peptidomimetic carrying a group G1 or G2 containing an appropriately protected alcohol group (e.g. as tert.-butyldiphenylsilyl protected), thiol group (e.g. as acetamidomethyl protected) or amino group (NR³⁴; e.g. as allyloxycarbonyl protected) can selectively be deprotected employing methods well known by the skilled in the art and reacted with suitably activated linker (L) precursors; e.g:

- 10 - for L1 the corresponding building block is Br(Cl,I)(CH₂)_pCHR⁶¹[X(CH₂)_pCHR⁶¹]_oOH: the resulting alcohol can be transformed into the corresponding bromide (chloride or iodide) by methods well known to those skilled in the art (e.g. P(Ph)₃, CBr₄) and combined with a second β -hairpin mimetic carrying a group G1 or G2 containing an alcohol, thiol or amine group. The dimeric fully side-chain protected molecule can be fully deprotected and purified by preparative HPLC chromatography as described in procedure 1, hereinbelow.
- 15 - for L2 the corresponding building block is ClOC(CH₂)_pCHR⁶¹[X(CH₂)_pCHR⁶¹]_oCOOAllyl: the resulting ester can be transformed into the corresponding acid by methods well known in the art and combined with a second β -hairpin mimetic carrying a group G1 or G2 containing an alcohol, thiol or amine group. The dimeric fully side-chain protected molecule can be fully deprotected and purified by preparative HPLC chromatography as described in procedure 1, hereinbelow.
- 20 - For L3 the corresponding building block is O=C=N(CH₂)_pCHR⁶¹[X(CH₂)_pCHR⁶¹]_oNR³⁴Alloc: the resulting Alloc-protected amine can be deprotected and transformed into the corresponding isocyanate by methods familiar to those skilled in the art (e.g. triphosgene) and combined with a second β -hairpin mimetic carrying a group G1 or G2 containing an alcohol, thiol or amine group. The dimeric fully side-chain protected molecule can be fully deprotected and purified by preparative HPLC chromatography as described in procedure 1, hereinbelow.
- 25 - For L7 the corresponding building block is Br(Cl,I)(CH₂)_oCHR⁶¹Y(CH₂)_oCHR⁶¹OH: the resulting alcohol can be transformed into the corresponding bromide (chloride or iodide) by methods well known in the art (e.g. P(Ph)₃, CBr₄) and combined with a second β -hairpin mimetic carrying a group G1 or G2 containing an alcohol, thiol or amine group. The dimeric fully side-chain protected molecule can be deprotected and purified by preparative HPLC chromatography as described in procedure 1, hereinbelow.
- 30 - For L8 the corresponding building block is ClOC(CH₂)_oCHR⁶¹Y(CH₂)_oCHR⁶¹COOAllyl: the resulting ester can be transformed into the corresponding acid by methods well known to those skilled in the art and combined with a second β -hairpin mimetic carrying a group
- 35

G1 or G2 containing an alcohol, thiol or amine group. The dimeric fully side-chain protected molecule can be deprotected and purified by preparative HPLC chromatography as described in procedure 1, hereinbelow.

- For L9 the corresponding building block is

5 $\text{O}=\text{C}=\text{N}(\text{CH}_2)_6\text{CHR}^{61}\text{Y}(\text{CH}_2)_6\text{CHR}^{61}\text{NR}^{34}\text{Alloc}$: the resulting Alloc-protected amine can be deprotected and transformed into the corresponding isocyanate by methods well known in the art (e.g. triphosgene) and combined with a second β -hairpin mimetic carrying a group G1 or G2 containing an alcohol, thiol or amine group. The dimeric fully side-chain protected molecule can be deprotected and purified by preparative HPLC chromatography as described in procedure 1, hereinbelow.

- For L13 the corresponding building block is

15 $\text{ClOC}(\text{CH}_2)_p\text{CHR}^{61}[\text{X}(\text{CH}_2)_p\text{CHR}^{61}]_n\text{NR}^{34}\text{Alloc}$: the resulting Alloc-protected amine can be deprotected by methods readily available to those skilled in the art and combined with a second β -hairpin mimetic carrying a group G1 or G2 containing a carboxylic acid group. The dimeric fully side-chain protected molecule can be deprotected and purified by preparative HPLC chromatography as described in procedure 1, hereinbelow.

- For L14 the corresponding building block is

20 $\text{ClOC}(\text{CH}_2)_6\text{CHR}^{61}\text{Y}(\text{CH}_2)_6\text{CHR}^{61}\text{NR}^{34}\text{Alloc}$: the resulting Alloc-protected amine can be deprotected by conventional methods and combined with a second β -hairpin mimetic carrying a group G1 or G2 containing a carboxylic acid group. The dimeric fully side-chain protected molecule can be deprotected and purified by preparative HPLC chromatography as described in procedure 1, hereinbelow.

Alternatively, a fully side-chain protected β -hairpin peptidomimetic carrying a group G1 or G2 containing an appropriately protected thiol group (e.g. as acetamidomethyl protected) can selectively be deprotected employing methods well known to those skilled in the art and reacted with a second β -hairpin peptidomimetic carrying a group G1 or G2 containing a thiol group forming a disulfide bond by oxidation (air or iodine). The dimeric molecule can subsequently be fully deprotected and purified by preparative HPLC chromatography as described in procedure 1, hereinbelow.

Finally, a fully side-chain protected β -hairpin peptidomimetic carrying a group G1 or G2 containing an appropriately protected carboxylic acid group (e.g. allyl ester), can selectively be deprotected employing methods well known in the art and reacted with a suitably activated linker (L) precursor; e.g:

- 5 - For L4 the corresponding building block is $\text{HO}(\text{CH}_2)_p\text{CHR}^{61}[\text{X}(\text{CH}_2)_p\text{CHR}^{61}]_n\text{OAlloc}$: the resulting Alloc-protected alcohol can be deprotected by methods well known to those skilled in the art and combined with a second β -hairpin mimetic carrying a group G1 or G2 containing a carboxylic acid group. The dimeric fully side-chain protected molecule can be deprotected and purified by preparative HPLC chromatography as described in procedure 1, hereinbelow.
- 10 - For L5 the corresponding building block is $\text{HS}(\text{CH}_2)_p\text{CHR}^{61}[\text{X}(\text{CH}_2)_p\text{CHR}^{61}]_n\text{SAlloc}$: the resulting Alloc-protected thiol can be deprotected by methods well known in the art and combined with a second β -hairpin mimetic carrying a group G1 or G2 containing a carboxylic acid group. The dimeric fully side-chain protected molecule can be deprotected and purified by preparative HPLC chromatography as described in procedure 1, hereinbelow.
- 15 - For L6 the corresponding building block is $\text{HNR}^{34}(\text{CH}_2)_p\text{CHR}^{61}[\text{X}(\text{CH}_2)_p\text{CHR}^{61}]_n\text{NR}^{34}\text{Alloc}$: the resulting Alloc-protected amine can be deprotected by methods familiar to those skilled in the art and combined with a second β -hairpin mimetic carrying a group G1 or G2 containing a carboxylic acid group. The dimeric fully side-chain protected molecule can be deprotected and purified by preparative HPLC chromatography as described in procedure 1, hereinbelow.
- 20 - For L10 the corresponding building block is $\text{HO}(\text{CH}_2)_n\text{CHR}^{61}\text{Y}(\text{CH}_2)_n\text{CHR}^{61}\text{OAlloc}$: the resulting Alloc-protected alcohol can be deprotected by methods well known to those skilled in the art and combined with a second β -hairpin mimetic carrying a group G1 or G2 containing a carboxylic acid group. The dimeric fully side-chain protected molecule can be deprotected and purified by preparative HPLC chromatography as described in procedure 1, hereinbelow.
- 25 - For L11 the corresponding building block is $\text{HS}(\text{CH}_2)_n\text{CHR}^{61}\text{Y}(\text{CH}_2)_n\text{CHR}^{61}\text{SAlloc}$: the resulting Alloc-protected thiol can be deprotected by methods well known in the art and combined with a second β -hairpin mimetic carrying a group G1 or G2 containing a carboxylic acid group. The dimeric fully side-chain protected molecule can be deprotected and purified by preparative HPLC chromatography as described in procedure 1, hereinbelow.
- 30 - For L12 the corresponding building block is $\text{HNR}^{34}(\text{CH}_2)_n\text{CHR}^{61}\text{Y}(\text{CH}_2)_n\text{CHR}^{61}\text{NR}^{34}\text{Alloc}$: the resulting Alloc-protected amine can be deprotected by methods well known to those skilled in the art and combined with a second β -hairpin mimetic carrying a group G1 or G2 containing a carboxylic acid group.
- 35 The dimeric fully side-chain protected molecule can be deprotected and purified by preparative HPLC chromatography as described in procedure 1, hereinbelow.

- For L15 the corresponding building block is
 $\text{HNR}^{34}(\text{CH}_2)_p\text{CHR}^{61}[\text{X}(\text{CH}_2)_p\text{CHR}^{61}]_o\text{COOAllyl}$: the resulting Allylester can be deprotected by conventional methods and combined with a second β -hairpin mimetic carrying a group G1 or G2 containing an alcohol group, a thiol group or an amino (NR^{34}) group. The dimeric fully side-chain protected molecule can be deprotected and purified by preparative HPLC chromatography as described in procedure 1, hereinbelow.
 - For L16 the corresponding building block is
 $\text{HNR}^{34}(\text{CH}_2)_o\text{CHR}^{61}\text{Y}(\text{CH}_2)_o\text{CHR}^{61}\text{COOAllyl}$: the resulting Allylester can be deprotected by methods well known to those skilled in the art and combined with a second β -hairpin mimetic carrying a group G1 or G2 containing an alcohol group, a thiol group or an amino (NR^{34}) group. The dimeric fully side-chain protected molecule can be deprotected and purified by preparative HPLC chromatography as described in procedure 1, hereinbelow.
- Finally, the fully protected peptide derivative of type Ia or Ib is treated with 95% TFA, 2.5% H_2O , 2.5% TIS or another combination of scavengers for effecting the cleavage of protecting groups. The cleavage reaction time is commonly 30 minutes to 12 hours, preferably about 2 hours. Thereafter most of the TFA is evaporated and the product is precipitated with ether/hexane (1:1) or other solvents which are suitable therefor. After careful removal of the solvent, the cyclic peptide derivative obtained as end-product can be isolated. Depending on its purity, this peptide derivative can be used directly for biological assays, or it has to be further purified, for example by preparative HPLC.

As mentioned earlier, it is thereafter possible, if desired, to convert a fully deprotected product thus obtained into a pharmaceutically acceptable salt or to convert a pharmaceutically acceptable, or unacceptable, salt thus obtained into the corresponding free compound of formula Ia and Ib or into a different, pharmaceutically acceptable, salt. Any of these operations can be carried out by methods well known in the art.

The starting materials used in the process of the invention, pre-starting materials therefor, and the preparation of these starting and pre-starting materials will now be discussed in detail.

- Building blocks of type A can be synthesized according to the literature methods described below. The corresponding amino acids have been described either as unprotected or as Boc- or Fmoc-protected racemates, (D)- or (L)-isomers. It will be appreciated that unprotected amino acid building blocks can be easily transformed into the corresponding Fmoc-protected amino acid building blocks required for the present invention by standard protecting group manipulations. Reviews describing general methods for the synthesis of α -amino acids include: R. Duthaler, *Tetrahedron (Report)* 1994, 349, 1540-1650; R. M. Williams, "Synthesis of optically active α -amino acids", *Tetrahedron Organic Chemistry Series*, Vol.7, J. E. Baldwin, P. D. Magnus (Eds.), Pergamon Press., Oxford 1989. An especially useful method for the synthesis of optically active α -amino acids relevant for this invention includes kinetic resolution using hydrolytic enzymes (M. A. Verhovskaya, I. A. Yamskov, *Russian Chem. Rev.* 1991, 60, 1163-1179; R. M. Williams, "Synthesis of optically active α -amino acids", *Tetrahedron Organic Chemistry Series*, Vol.7, J. E. Baldwin, P. D. Magnus (Eds.), Pergamon Press., Oxford 1989, Chapter 7, p.257-279). Hydrolytic enzymes involve hydrolysis of amides and nitriles by aminopeptidases or nitrilases, cleavage of N-acyl groups by acylases, and ester hydrolysis by lipases or proteases. It is well documented that certain enzymes will lead specifically to pure (L)-enantiomers whereas others yield the corresponding (D)-enantiomers (e.g. : R. Duthaler, *Tetrahedron Report* 1994, 349, 1540-1650; R. M. Williams, "Synthesis of optically active α -amino acids", *Tetrahedron Organic Chemistry Series*, Vol.7, J. E. Baldwin, P. D. Magnus (Eds.), Pergamon Press., Oxford 1989).
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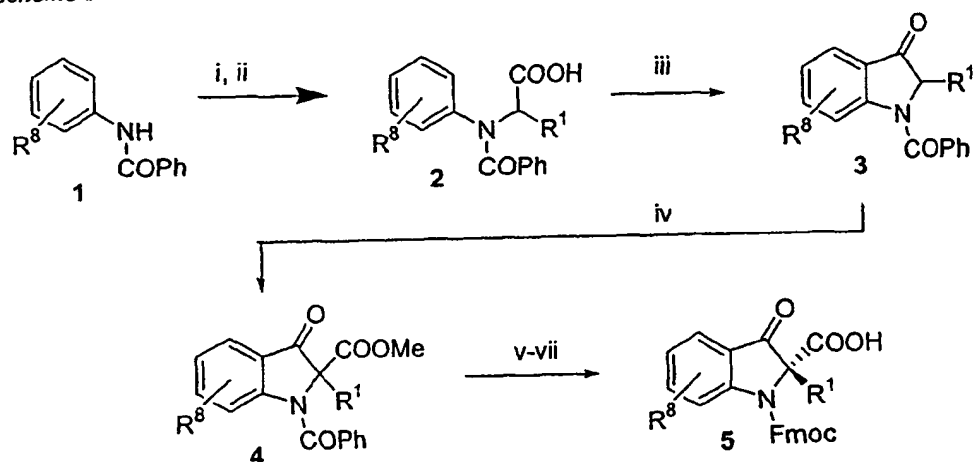
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- A12: See Ahmed, Cheeseman, *Tetrahedron* 1977, 33, 2255-2257; J. S. New, J. P. Yevich, *J. Heterocycl. Chem.* 1984, 21, 1355-1360; R. Kikumoto, Y. Tamao, K. Ohkubo, T. Tezuka, S. Tonomura, *J. Med. Chem.* 1980, 23, 1293-1299; C. J. Blankley, J. S. Kaltenbronn, D. E. DeJohn, A. Werner, L. R. Bennett, *J. Med. Chem.* 1987, 30, 992-998; S. Klutcho, C. J. Blankley, R. W. Fleming, J. M. Hinkley, R. E. Werner, *J. Med. Chem.* 1986, 29, 1953-1961

(R¹=H; R⁸=H); L. J. Beeley, C. J. M. Rockwell, *Tetrahedron Lett.* 1990, 31, 417-420 (R¹=COOEt; R⁸=H).

- A13: See G. Flouret, W. Briher, T. Majewski, K. Mahan, *J. Med. Chem.* 1991, 43, 2089-2094; G. Galiendo, P. Grieco, E. Perissuti, V. Santagada, *Farmaco*, 1996, 51, 197-202; D. F. McComsey, M. J. Hawkins, P. Andrade-Gordon, M. F. Addo, B. E. Maryanoff, *Bioorg. Med. Chem. Lett.* 1999, 9, 1423-1428; G. B. Jones, S. B. Heaton, B. J. Chapman, M. Guzel, *Tetrahedron: Asymmetry* 1997, 8, 3625-3636; M. Asami, H. Watanabe, K. Honda, S. Inoue, *Tetrahedron: Asymmetry* 1998, 9, 4165-4174; K. Gross, Y. M. Yun, P. Beak, *J. Org. Chem.* 1997, 62, 7679-7689 (R¹=H; R⁶=H; R⁸=H); K. Gross, Y. M. Yun, P. Beak, *J. Org. Chem.* 1997, 62, 7679-7689 (R¹=H; R⁶=H; R⁸=6-Cl); Ch. Noe, M. Knollmueller, C. Schoedl, M. L. Berger, *Sci. Pharm.* 1996, 64, 577-590; E. Reiman, W. Erdle, H. Unger, *Pharmazie*, 1994, 54, 418-421 (R¹=H; R⁶=CH₂COOH; R⁸=H); V. Collot, M. Schmitt, A. K. Marwah, B. Norberg, J.-J. Bourignon, *Tetrahedron Lett.* 1997, 38, 8033-8036 (R¹=H; R⁶=Ph; R⁸=H); L. V. Dunkerton, H. Chen, B. P. McKillican, *Tetrahedron Lett.* 1988, 29, 2539-2542 (R¹=C(CH₃)₂CH=CH₂; R⁶=H; R⁸=H); E. J. Corey, *J. Am. Chem. Soc.* 1970, 92, 2476-2488; Neunhoeffter, Lehmann, *Chem. Ber.* 1961, 94, 2960-2963 (R¹=CH₃; R⁶=H; R⁸=H).

A14: Amino acids of type A14 can be made according to *Scheme 1*.

Scheme 1



i: NaH, $\text{BrCH(R}^1\text{)COOMe}$, DMF; ii: $\text{LiOH}\cdot\text{xH}_2\text{O}$, MeOH, H_2O ; iii: polyphosphoric acid(PPA);
 iv: NaH, ClCOOMe , THF; v: enzymatic resolution (e.g. lipase); vi: NaOH, MeOH, H_2O , heat;
 vii: FmocOSu , $\text{Na}_2\text{CO}_3\text{aq.}$, dioxane

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A15: See D. S. Perlow, J. M. Erb, N. P. Gould, R. D. Tung, R. M. Freidinger, *J. Org. Chem.* 1992, 57, 4394-4400; D. Y. Jackson, C. Quan, D. R. Artis, T. Rawson, B. Blackburn, *J. Med. Chem.* 1997, 40, 3359-3368 ($\text{R}^1 = \text{H}$; $\text{R}^2 = \text{H}$); H. H. Wasserman, K. Rodrigues, K. Kucharczyk, *Tetrahedron Lett.* 1989, 30, 6077-6080 ($\text{R}^1 = \text{H}$; $\text{R}^2 = \text{COOH}$).

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A16: See Beyerman, Boekee, *Recl. Trav. Chim. Pays-Bas*, 1959, 78, 648-653; M. E. Freed, A. R. Day, *J. Org. Chem.* 1960, 25, 2105-2107; D. R. Adams, P. D. Bailey, I. D. Collier, J. D. Heferman, S. Slokes, *J. Chem. Soc. Chem. Commun.* 1996, 349-350; J. E. Baldwin, R. M. Adlington, C. R. A. Godfrey, D. W. Collins, J. D. Vaughan, *J. Chem. Soc. Chem. Commun.* 1993, 1434-1435; Y. Matsumura, Y. Takeshima, H. Ohita, *Bull. Chem. Soc. Jpn.* 1994, 67, 304-306 ($\text{R}^1 = \text{H}$; $\text{R}^6 = \text{H}$); C. Herdeis, W. Engel, *Arch. Pharm.* 1991, 324, 670 ($\text{R}^1 = \text{COOMe}$; $\text{R}^6 = \text{CH}_3$).

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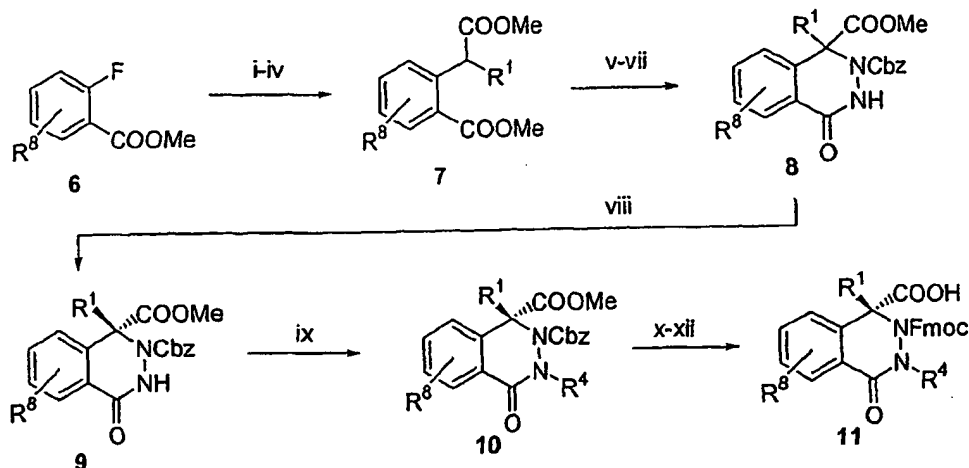
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5 O Bn); T. Kamenecka, S. J. Danishefsky, *Angew. Chem. Int. Ed. Engl.* 1998, 37, 2995-2998 ($R^1 = H$; $R^3 = COO(CH_2)_2SiMe_3$; $R^5 = OSiMe_2tBu$).

A19: See Beilstein, Registry Number 648833 ($R^1=R^4=R^8=H$). Compounds of this type can be prepared according to Scheme 2.

5 Scheme 2.



i: NaH, $\text{CH}_2(\text{COOMe})_2$, DMSO; ii: NaH, R^1-X , DMSO; iii: NaOH aq., MeOH, 75°; iv: DBU, MeI, DMF; v: LDA, $\text{BocN}=\text{NBoc}$; vi: TFA, CH_2Cl_2 ; vii: CbzCl, Na_2CO_3 aq., dioxane; viii: enzymatic resolution (e.g. lipase); then DBU, MeI, DMF; ix: NaH, R^4-X , THF; x: Pd/C, H_2 , EtOH; xi: $\text{LiOH} \cdot \text{H}_2\text{O}$, MeOH, H_2O ; xii: FmocOSu, Na_2CO_3 aq., dioxane

A20: See D. Hagiwara, H. Miyake, N. Igari, M. Karino, Y. Maeda, *J. Med. Chem.* 1994, 37, 2090-2099 ($R^1=H$; $R^9=OH$); Y. Arakawa, M. Yasuda, M. Ohnishi, S. Yoshifuji, *Chem.*

- 10 *Pharm. Bull.* 1997, 45, 255-259 ($R^1=H$; $R^9=COOH$); P. J. Murray, I. D. Starkey, *Tetrahedron Lett.* 1996, 37, 1875-1878 ($R^1=H$; $R^9=(\text{CH}_2)_2\text{NHCOCH}_2\text{Ph}$); K. Clinch, A. Vasella, R. Schauer, *Tetrahedron Lett.* 1987, 28, 6425-6428 ($R^1=H$; $R^9=\text{NHAc}$).

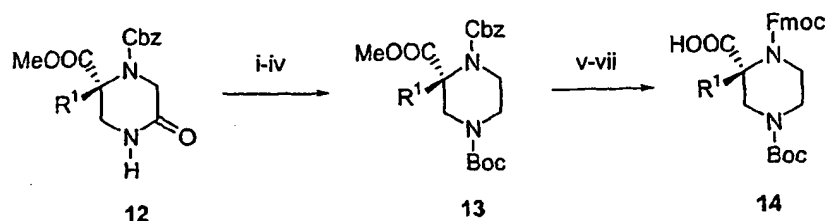
A21: See A. Golubev, N. Sewald, K. Burger, *Tetrahedron Lett.* 1995, 36, 2037-2040; F.

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- A23: See Beyerman, Boeke, *Recl. Trav. Chim. Pays-Bas* **1959**, 78, 648-653; D. R. Adams, P. D. Bailey, I. D. Collier, J. D. Heffernan, S. Stokes *J. Chem. Soc. Chem. Commun.* **1996**, 349-350; J. E. Baldwin, R. M. Adlington, C. Godfrey, D. W. Collins, J. G. Vaughan, *J. Chem. Soc. Chem. Commun.* **1993**, 1434-1435 ($R^1 = R^6 = H$); C. Herdeis, W. Engel, *Arch. Pharm.* **1993**, 297-302 ($R^1 = \text{COOMe}$; $R^6 = H$).
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- 15 McElvain, Laughton, *J. Am. Chem. Soc.* **1951**, 73, 448-451 ($R^1 = \text{Ph}$; $R^6 = H$);
- A25: See L.-Y. Hu, T. R. Ryder, S. S. Nikam, E. Millerman, B. G. Szoke, M. F. Rafferty, *Bioorg. Med. Chem. Lett.* **1999**, 9, 1121-1126; W. C. Lumma, R. D. Hartman, W. S. Saari, E. L. Engelhardt, V. J. Lotti, C. A. Stone, *J. Med. Chem.* **1981**, 24, 93-101; N. Hosten, M. J. O.
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- 25 Keane, *J. Med. Chem.* **1999**, 42, 5254-5265 ($R^1 = H$; $R^{11} = H$); B. D. Dorsey, R. B. Levin, S. L. McDaniel, J. P. Vacca, J. P. Guare, *J. Med. Chem.* **1994**, 37, 3443-3451; M. Cheng, B. De, S. Pikul, N. G. Almstaed, M. G. Natchus, M. V. Anastasio, S. J. McPhail, C. J. Snider, Y. O. Taiwo, L. Chen, C. M. Dunaway, *J. Med. Chem.* **2000**, 43, 369-380; R. Kuwano, Y. Ito, *J. Org. Chem.* **1999**, 64, 1232-1237 ($R^1 = H$; $R^{11} = \text{COOtBu}$); J. Kitchin, R. C. Bethell, N.
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Compounds of type A25 can also be prepared according to *Scheme 3*:

Scheme 3



i: Lawesson reagent, toluene, 80°; ii: DBU, MeI, DMF; iii: NaBH₄ or NaCNBH₃, MeOH; iv: Boc₂O, THF; v: LiOHx1H₂O, MeOH, H₂O; vi: Pd/C, H₂, EtOH; vii: FmocOSu, Na₂CO₃aq., dioxane

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A26: See Koegel, *J. Biol. Chem.* 1953, 201, 547 ($R^1=R^2=H$).

A27: Sec G. Makara, G. R. Marshall, *Tetrahedron Lett.* 1997, 38, 5069-5072; R. N. Patel, A. Banerjee, R. L. Hanson, D. B. Brzozowski, L. W. Parker, L. J. Szarka, *Tetrahedron*:

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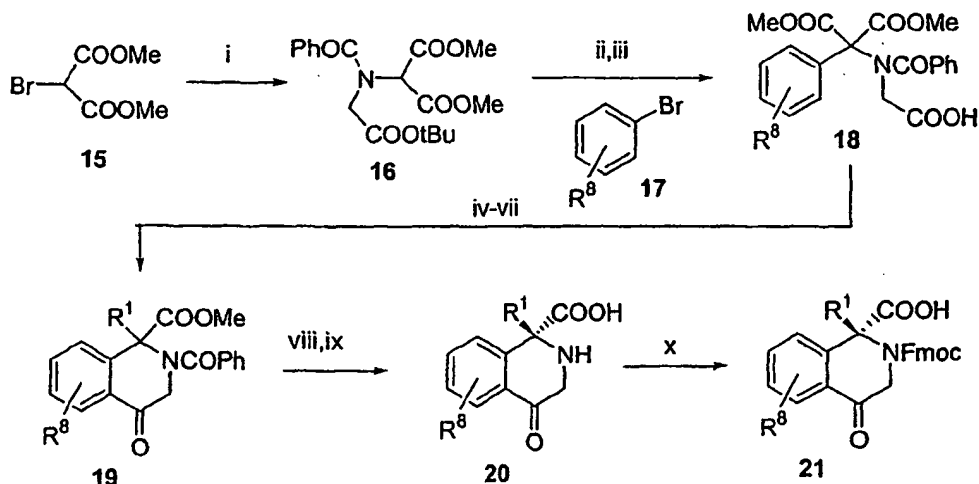
A29: See Kawase, Masami, *Chem. Pharm. Bull.* **1997**, *45*, 1248-1253; I. G. C. Coutts, J. A. Hadfield, P. R. Huddleston, *J. Chem. Res. Miniprint*, **1987**, *9*, 2472-2500; I. G. C. Coutts, J. A. Hadfield, P. R. Huddleston, *J. Chem. Res. Miniprint*, **1987**, *9*, 2472-2500; V. J. Hruby, W. L. Cody, A. M. Castrucci, M. E. Hadley, *Collect. Czech. Chem. Commun.* **1988**, *53*, 2549-2573; R. T. Shuman, R. B. Rothenberger, C. S. Campbell, G. F. Smith, D. S. Gifford-Moore, P. D. Gesellchen, *J. Med. Chem.* **1993**, *36*, 314-319; M. Kawase, Y. Okada, H. Miyamae, *Heterocycles*, **1998**, *48*, 285-294 ($R^1=R^8=H$); Kawase, Masami, *Chem. Pharm. Bull.* **1997**, *45*, 1248-1253 ($R^1=H$; $R^8=6,7-(MeO)_2$); D. F. Ortwine, T. C. Malone, C. F. Bigge, J. T. Drummond, C. Humblet, *J. Med. Chem.* **1992**, *35*, 1345-1370 ($R^1=H$; $R^8=7-CH_2PO(OEt)_2$); E. J. Corey, D. Y. Gin, *Tetrahedron Lett.* **1996**, *37*, 7163-7166 ($R^1=CH_2SCOOtBu$); P. Dostert,

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- 5 Chrzanowska, B. Schönenberger, A. Brossi, J. L. Flippen-Anderson, *Helv. Chim. Acta* **1987**, *70*, 1721-1731; T. Hudlicky, *J. Org. Chem.* **1981**, *46*, 1738-1741 ($R^1=Bn$; $R^8=6,7-(OH)_2$); A. I. Meyers, M. A. Gonzalez, V. Struzka, A. Akahane, J. Guiles, J. S. Warmus, *Tetrahedron Lett.* **1991**, *32*, 5501-5504 ($R^1=CH_2(3,4\text{-methylenedioxy})C_6H_3$; $R^8=6,7-(OMe)_2$).

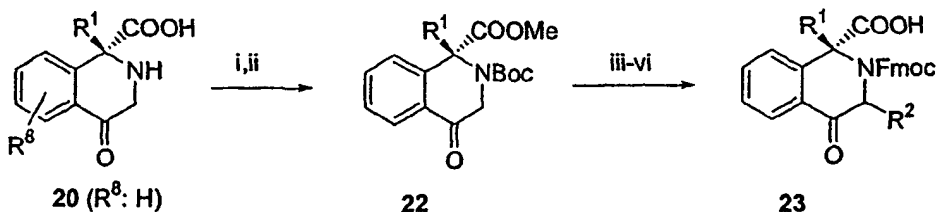
A30 and A31 can be prepared according to *Schemes 4 and 5*.

5 *Scheme 4*



i: NaH, tert.-butyl N-benzoyl glycinate, DMF; ii: NaH, Pd(0), toluene; iii: TFA, CH₂Cl₂; iv: polyphosphoric acid; v: NaOHaq., MeOH, 75°; then HClaq.; vi: DBU, MeI, DMF; vii: lithium hexamethyldisilazide, THF, chlorotrimethylsilane, -78°; then R¹-X; viii: enzymatic resolution (e.g. lipase); then isolation as methylester: DBU, MeI, DMF; ix: NaOHaq., MeOH, heat; x: FmocOSu, Na₂CO₃aq., dioxane

Scheme 5



i: Boc₂O, Na₂CO₃aq., dioxane; ii: DBU, MeI, DMF; iii: lithium hexamethyldisilazide, THF, chlorotrimethylsilane, -78°; then R²-X; iv: LiOHx1H₂O, MeOH, H₂O; v: TFA, CH₂Cl₂; vi: FmocOSu, Na₂CO₃aq., dioxane

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A32 can be prepared according to P. W. Schiller, G. Weltrowska, T. M.-D. Nguyen, C.

Lemieux, N. Nga, *J. Med. Chem.* 1991, 34, 3125-3132; V. S. Goodfellow, M. V. Marathe, K.

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- (R¹=R⁸=H); D. Tourwe, E. Mannekens, N. T. Trang, P. Verheyden, H. Jaspers, *J. Med. Chem.* **1998**, *41*, 5167-5176; A.-K. Szardenings, M. Gordeev, D. V. Patel, *Tetrahedron Lett.* **1996**, *37*, 3635-3638; W. Wicz, K. Stachowiak, P. Skurski, L. Lankiewicz, A. Michniewicz, A. Roy, *J. Am. Chem. Soc.* **1996**, *118*, 8300-8307; K. Verschuren, G. Toth, D. Tourwe, M. Lebl., G. van Binst, V. Hrubí, *Synthesis* **1992**, 458-460 (R¹=H; R⁸=6-OH); P. L. Ornstein, M. B. Arnold, N. K. Augenstein, J. W. Paschal, *J. Org. Chem.* **1991**, *56*, 4388-4392 (R¹=H; R⁸=6-MeO); D. Ma, Z. Ma, A. P. Kozikowski, S. Pshenichkin, J. T. Wroblewski, *Bioorg. Med. Lett.* **1998**, *8*, 2447-2450 (R¹=H; R⁸=6-COOH); U. Schöllkopf, R. Hinrichs, R. Lonsky, *Angew. Chem.* **1987**, *99*, 137-138 (R¹=Me; R⁸=H); B. O. Kammermeier, U. Lerch, C. Sommer, *Synthesis* **1992**, 1157-1160 (R¹=COOMe; R⁸=H); T. Gees, W. B. Schweizer, D. Seebach, *Helv. Chim. Acta* **1993**, *76*, 2640-2653 (R¹=Me; R⁸=6,7-(MeO₂)).

A33: See Hinton, Mann, *J. Chem. Soc.* **1959**, 599-608.

- 15 A34: See G. P. Zecchini, M. P. Paradisi, *J. Heterocycl. Chem.* **1979**, *16*, 1589-1597; S. Cerrini, *J. Chem. Soc. Perkin Trans.1*, **1979**, 1013-1019; P. L. Ornstein, J. W. Paschal, P. D. Gesellchen, *J. Org. Chem.* **1990**, *55*, 738-741; G. M. Ksander, A. M. Yan, C. G. Diefenbacher, J. L. Stanton, *J. Med. Chem.* **1985**, *28*, 1606-1611; J. A. Robl, D. S. Karanewsky, M. M. Asaad, *Tetrahedron Lett.* **1995**, *36*, 1593-1596; S. Katayama, N. Ae, R. Nagata, *Tetrahedron: Asymmetry* **1998**, *9*, 4295-4300 (R¹=R⁸=H); K. Hino, Y. Nagai, H. Uno, *Chem. Pharm. Bull.* **1988**, *36*, 2386-2400 (R¹=Me; R⁸=H).

A35: See Beilstein Registry Numbers: 530775, 883013 (R¹=R⁸=H).

- 25 A36: See R. W. Carling, P. D. Leeson, A. M. Moseley, R. Baker, A. C. Foster, *J. Med. Chem.* **1992**, *35*, 1942-1953; S. Kano, T. Ebata, S. Shibuya, *J. Chem. Soc. Perkin Trans.1*, **1980**, 2105-2111 (R¹=R⁸=H); R. W. Carling, P. D. Leeson, A. M. Moseley, R. Baker, A. C. Foster, *J. Med. Chem.* **1992**, *35*, 1942-1953 (R¹=H; R⁸=5-Cl; 7-Cl).

- 30 A37: See Nagarajan, *Indian J. Chem.* **1973**, *11*, 112 (R¹=CH₂COOMe; R⁸=H).

A38: See R. Pauly, N. A. Sasaki, P. Potire, *Tetrahedron Lett.* **1994**, *35*, 237-240; J. Podlech, D. Seebach, *Liebigs Ann. Org. Bioorg. Chem.* **1995**, *7*, 1217-1228; K. C. Nicolaou, G.-Q. Shi, K. Namoto, F. Bernal, *J. Chem. Soc. Chem. Commun.* **1998**, 1757-1758 (R¹=H; R²=H).

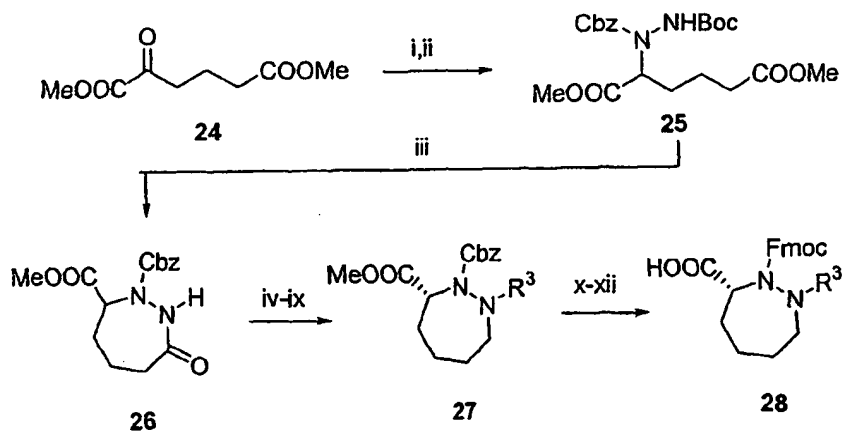
35

A39: See Beilstein, Registry Number 782885.

A40: See F. P. J. C. Rutjes, N. M. Terhuis, H. Hiemstra, N. W. Speckamp, *Tetrahedron* 1993, 49, 8605-8628 ($R^1 = H$; $R^3 = Bn$); compounds of this type can be prepared according to Scheme 6

5 6.

Scheme 6

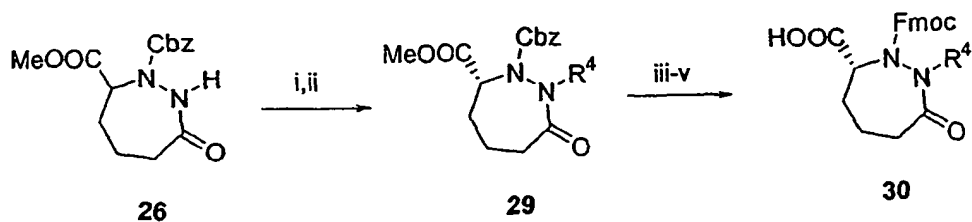


i: BocNHNH_2 , NaCNBH_3 , MeOH, AcOH; ii: CbzCl , Et_3N , CH_2Cl_2 ; iii: TFA, CH_2Cl_2 ; then pyridine, DMAP, heat; iv: resolution (e.g. lipase); v: DBU, MeI, DMF; vi: Lawesson reagent, toluene, 75° ; vii: DBU, MeI, DMF; viii: NaBH_4 or NaCNBH_3 , MeOH; ix: R^3 introduced by reductive amination, alkylation or acylation; x: $\text{LiOH} \cdot \text{H}_2\text{O}$, MeOH, H_2O ; xi: Pd/C, H_2 , EtOH; xii: FmocOSu , Na_2CO_3 aq., dioxane

A41: Compounds of this type can be prepared according to *Scheme 7*.

Scheme 7

5



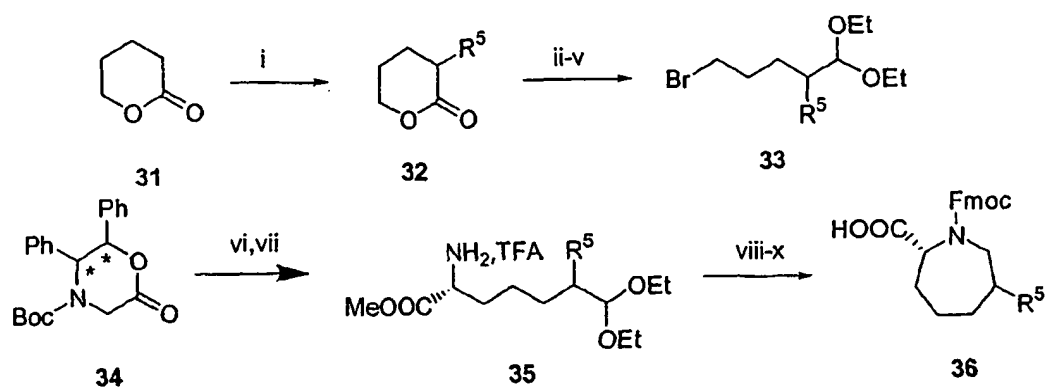
i: resolution (e.g. lipase); then isolation as methylester: DBU, MeI, DMF;
 ii: NaH, R⁴-X, THF; iii: LiOHx1H₂O, MeOH, H₂O; iv: Pd/C, H₂, EtOH;
 v: FmocOSu, Na₂CO₃aq., dioxane

A42 to A46: Compounds of this type can be prepared according to *Scheme 8 to 12*. Key intermediate **34** and α -amino acid synthesis involving this building block include: R. M.

- 10 Williams, M.-N. Im, *Tetrahedron Lett.* **1988**, *29*, 6079-6082; R. M. Williams, M.-N. Im, *J. Am. Chem. Soc.* **1991**, *113*, 9276-9286; J. F. Dellaria, B. D. Santarsiero, *Tetrahedron Lett.* **1988**, *29*, 6079-6082; J. F. Dellaria, B. D. Santarsiero, *J. Org. Chem.* **1989**, *54*, 3916-3926; J. E. Baldwin, V. Lee, C. J. Schofield, *Synlett* **1992**, 249-251; J. E. Baldwin, V. Lee, C. J. Schofield, *Heterocycles* **1992**, *34*, 903-906.

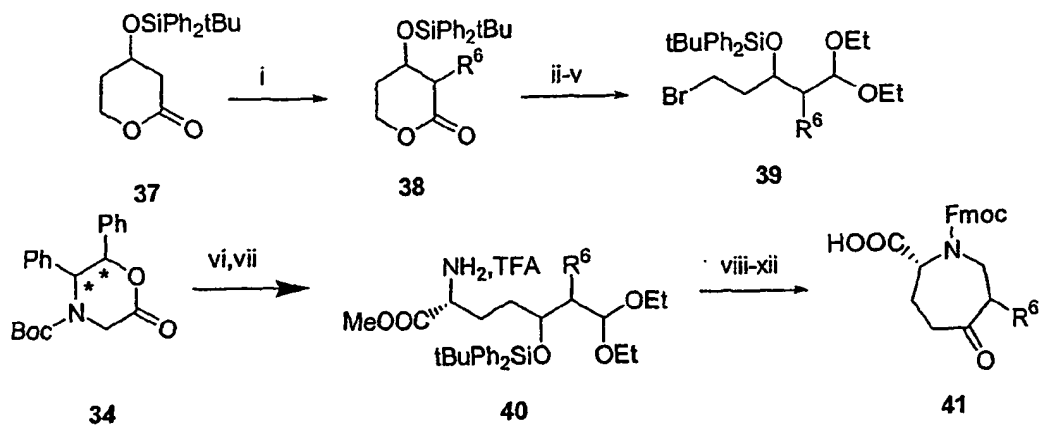
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Scheme 8



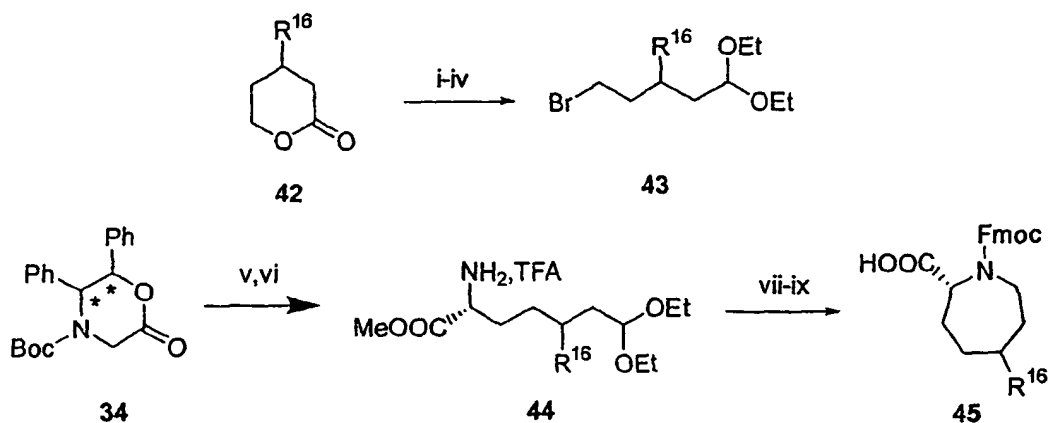
i: lithium hexamethyldisilazide, THF, chlorotrimethylsilane, -78° ; then R^5 -X; ii: HBr; iii: DBU, MeI, DMF; iv: DIBAL-H, THF; v: EtOH, pyridinium p-toluenesulfonate, mol.sieves 4A; vi: lithium hexamethyldisilazide, THF, -78° , 33; vii: Pd/C, H_2 , EtOH; then DBU, MeI, DMF; then TFA, CH_2Cl_2 ; viii: HCl aq., THF; then $Na(OAc)_3BH$, AcOH, dichloroethane; ix: $LiOH \cdot xH_2O$, MeOH, H_2O ; x: FmocOSu, Na_2CO_3 aq., dioxane

5 Scheme 9



i: lithium hexamethyldisilazide, THF, chlorotrimethylsilane, -78° ; then R^6 -X; ii: HBr; iii: DBU, MeI, DMF; iv: DIBAL-H, THF; v: EtOH, pyridinium p-toluenesulfonate, mol.sieves 4A; vi: lithium hexamethyldisilazide, THF, -78° , 39; vii: Pd/C, H_2 , EtOH; then DBU, MeI, DMF; then TFA, CH_2Cl_2 ; viii: HCl aq., THF; then $Na(OAc)_3BH$, AcOH, dichloroethane; viii: Boc_2O , Et_3N , CH_2Cl_2 ; ix: $Bu_4NF \cdot xH_2O$, THF; ix: pyridinium chlorochromate; x: $LiOH \cdot xH_2O$, MeOH, H_2O ; xi: TFA, CH_2Cl_2 ; xii: FmocOSu, Na_2CO_3 aq., dioxane

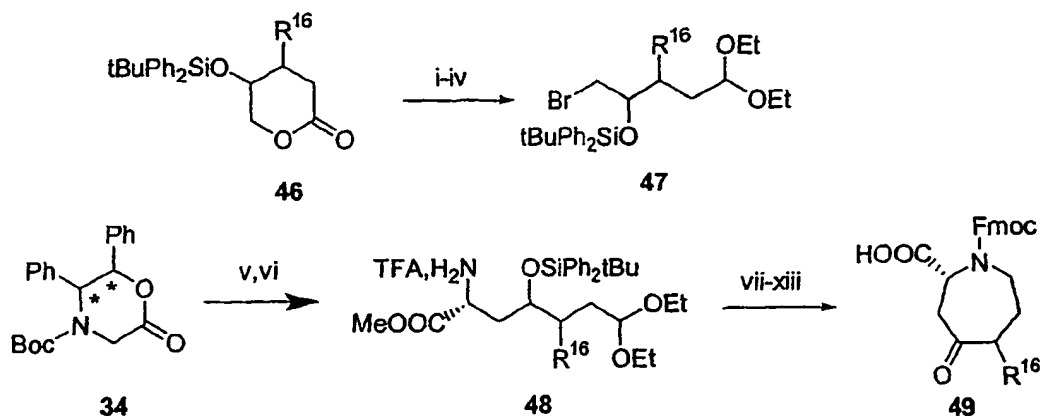
Scheme 10



i: HBr; ii: DBU, MeI, DMF; iii: DIBAL-H, THF; iv: EtOH, pyridinium p-toluenesulfonate, mol. sieves 4A; v: lithium hexamethyldisilazide, THF, -78°, 43; vi: Pd/C, H₂, EtOH; then DBU, MeI, DMF; then TFA, CH₂Cl₂; vii: HCl aq., THF; then Na(OAc)₃BH, AcOH, dichloroethane; viii: LiOH·xH₂O, MeOH, H₂O; ix: FmocOSu, Na₂CO₃ aq., dioxane

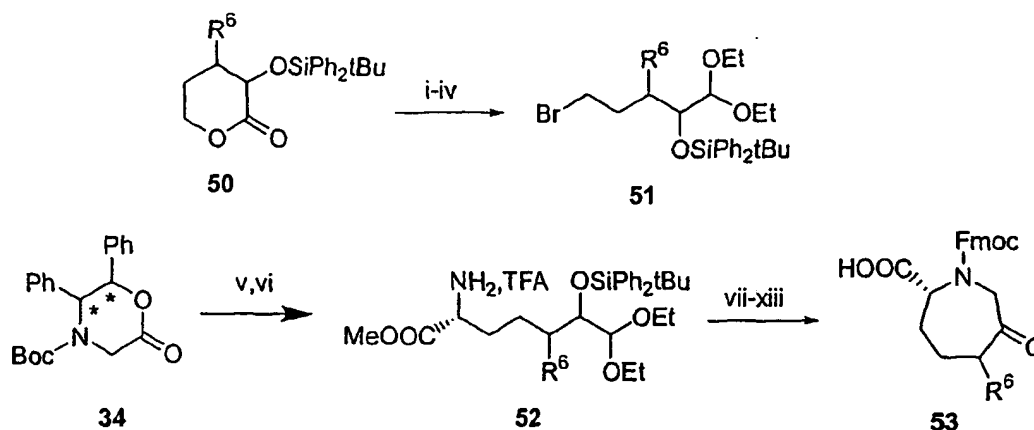
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Scheme 11



i: HBr; ii: DBU, MeI, DMF; iii: DIBAL-H, THF; iv: EtOH, pyridinium p-toluenesulfonate, mol. sieves 4A; v: lithium hexamethyldisilazide, THF, -78°, 47; vi: Pd/C, H₂, EtOH; then DBU, MeI, DMF; then TFA, CH₂Cl₂; vii: HCl aq., THF; then Na(OAc)₃BH, AcOH, dichloroethane; viii: Boc₂O, Et₃N, CH₂Cl₂; ix: Bu₄NF·xH₂O, THF; x: pyridinium chlorochromate; xi: LiOH·xH₂O, MeOH, H₂O; xii: TFA, CH₂Cl₂; xiii: FmocOSu, Na₂CO₃ aq., dioxane

Scheme 12



i: HBr; ii: DBU, MeI, DMF; iii: DIBAL-H, THF; iv: EtOH, pyridinium p-toluenesulfonate, mol. sieves 4A; v: lithium hexamethyldisilazide, THF, -78°, 51; vi: Pd/C, H₂, EtOH; then DBU, MeI, DMF; then TFA, CH₂Cl₂; vii: HCl aq., THF; then Na(OAc)₃BH, AcOH, dichloroethane; viii: Boc₂O, Et₃N, CH₂Cl₂; ix: Bu₄NF·10H₂O, THF; x: pyridinium chlorochromate; xi: LiOH·H₂O, MeOH, H₂O; xii: TFA, CH₂Cl₂; xiii: FmocOSu, Na₂CO₃ aq., dioxane

- 5 A47: See P. Barraclough, R. D. Farrant, D. Kettle, S. Smith, *J. Chem. Res. Miniprint* 1991, 11, 2876-2884 (R¹=R¹¹=H, Bn, (CH₂)₂PO(OEt)₂).

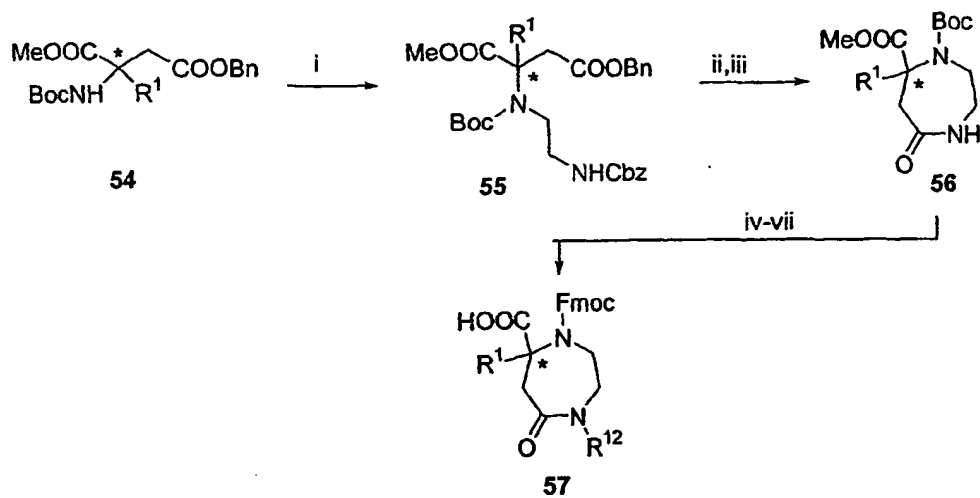
A48: See A. Nouvet, M. Binard, F. Lamaty, J. Martinez, R. Lazaro, *Tetrahedron* 1999, 55, 4685-4698 (R¹=R¹²=H).

10

A49: See M. Y. Kolleganov, I. G. Kolleganova, M. D. Mitrofanova, L. I. Martynenko, P. P. Nazarov, V. I. Spitsyn, *Bull. Acad. Sci. USSR Div. Chem. Sci (Engl. Trans.)* 1983, 32, 1293-1299; *Izv. Akad. Nauk SSSR Ser. Khim.* 1983, 6, 1293-1299; V. P. Vasilev, T. D. Orlova, S. F. Ledenkov, *J. Gen. Chem. USSR (Engl. Trans.)* 1989, 59, 1629-1634; *Zh. Obshch. Khim.*

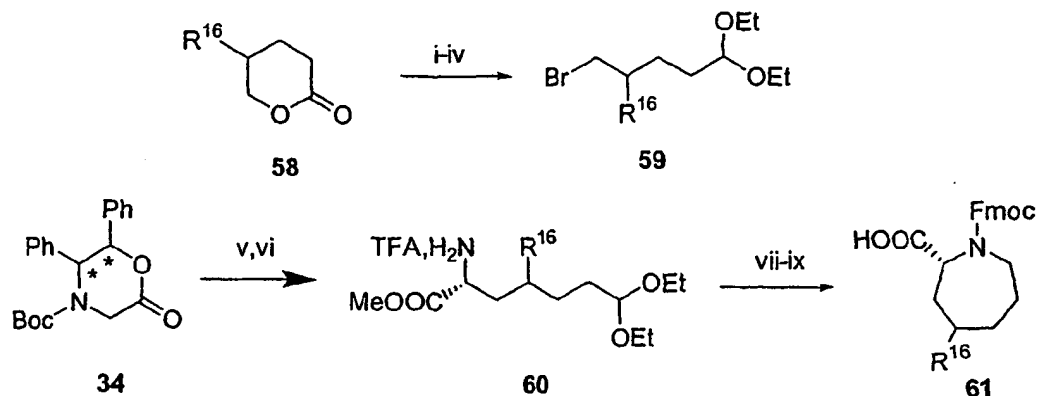
- 15 1989, 59, 1828-1833 (R¹=H; R¹²=CH(COOH)CH₂COOH). Compounds of type A49 can also be prepared according to Scheme 13.

Scheme 13



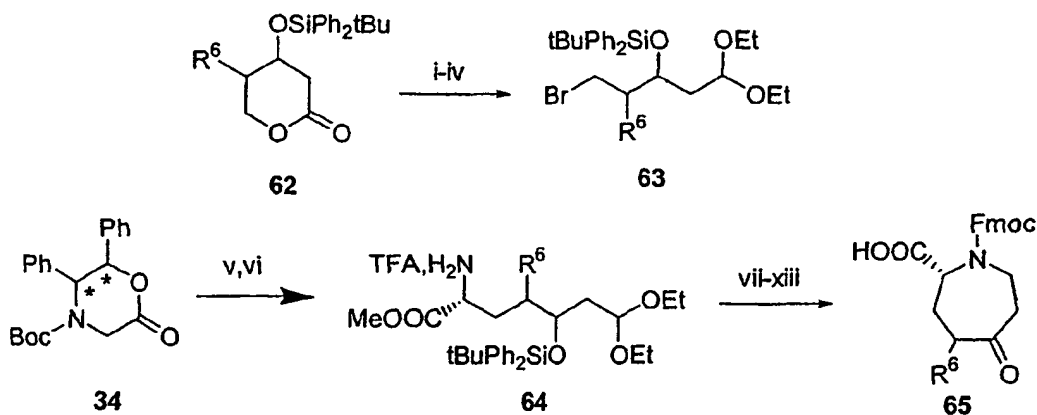
i: NaH, CbzNH(CH₂)₂Br, THF; ii: Pd/C, H₂, EtOH; iii: EDCI, CH₂Cl₂, diisopropylethylamin; iv: NaH, R¹²-X, THF; v: LiOHx1H₂O, MeOH, H₂O; vi: TFA, CH₂Cl₂; vii: FmocOSu, Na₂CO₃aq., dioxane

A50 and A51: Compounds of these types can be prepared according to *Schemes 14* and *15*.
Scheme 14



i: HBr; ii: DBU, MeI, DMF; iii: DIBAL-H, THF; iv: EtOH, pyridinium *p*-toluenesulfonate, mol. sieves 4A; v: lithium hexamethyldisilazide, THF, -78°, 59; vi: Pd/C, H₂, EtOH; then DBU, MeI, DMF; then TFA, CH₂Cl₂; vii: HCl aq., THF; then Na(OAc)₃BH, AcOH, dichloroethane; viii: LiOH·H₂O, MeOH, H₂O; ix: FmocOSu, Na₂CO₃ aq., dioxane

Scheme 15

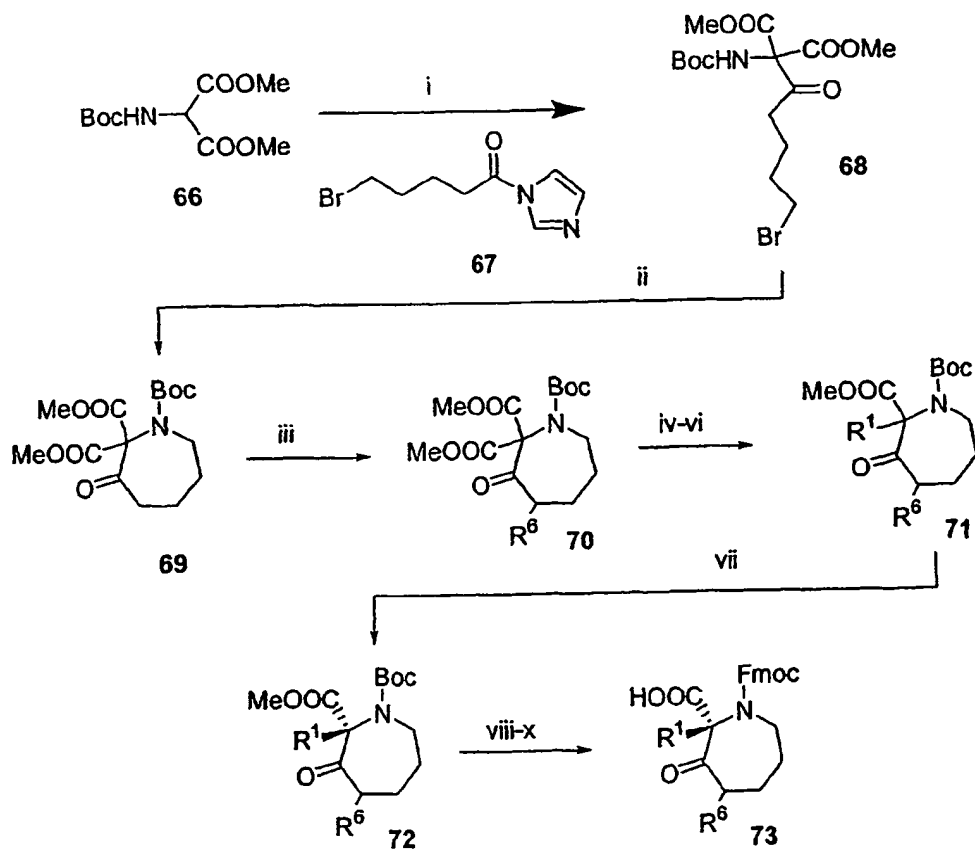


i: HBr; ii: DBU, MeI, DMF; iii: DIBAL-H, THF; iv: EtOH, pyridinium *p*-toluenesulfonate, mol. sieves 4A; v: lithium hexamethyldisilazide, THF, -78°, 63; vi: Pd/C, H₂, EtOH; then DBU, MeI, DMF; then TFA, CH₂Cl₂; vii: HCl aq., THF; then Na(OAc)₃BH, AcOH, dichloroethane; viii: Boc₂O, Et₃N, CH₂Cl₂; ix: Bu₄NF·10H₂O, THF; x: pyridinium chlorochromate; xi: LiOH·H₂O, MeOH, H₂O; xii: TFA, CH₂Cl₂; xiii: FmocOSu, Na₂CO₃ aq., dioxane

- 10 A53: See P. Barraclough, R. D. Farrant, D. Kettle, S. Smith, *J. Chem. Res. Miniprint* 1991, 11, 2876-2884 (R¹=R¹¹=H; R¹=H; R¹¹=Bn, (CH₂)₃PO(OH)₂; (CH₂)₃PO(Et)₂); J. I. Levin, J. F. DiJoseph, L. M. Killar, A. Sung, T. Walter, *Bioorg. Med. Chem. Lett.* 1998, 8, 2657-2662 (R¹=H; R¹¹=4CF₃OC₆H₄CO).

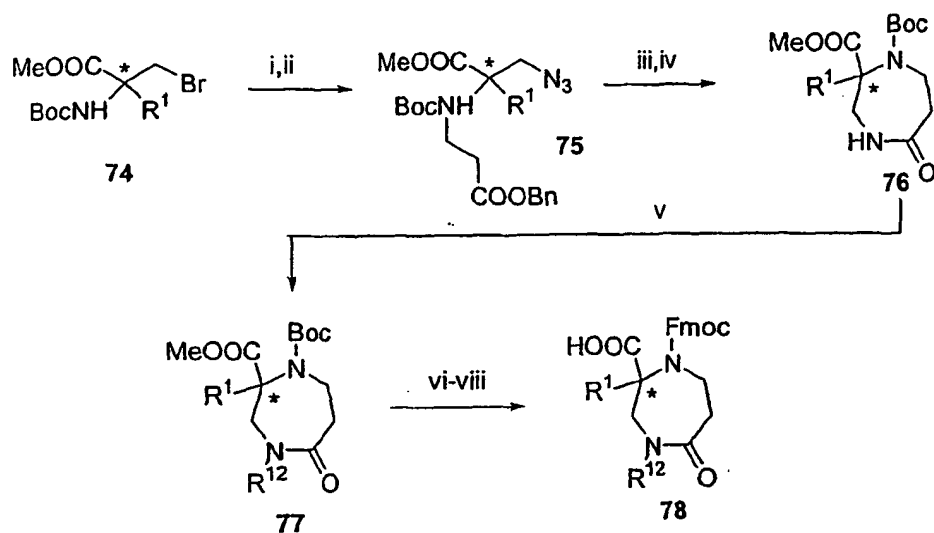
A 52 and A54: Compounds of this type can be prepared according to *Schemes 16 and 17*.

Scheme 16



i: *i*BuMgCl, THF; ii: NaH, THF; iii: lithium hexamethyldisilazide, THF, chlorotrimethylsilane, -78°; then R⁶-X; iv: NaOHaq., MeOH, 75°; then HCl aq.; v: DBU, MeI, DMF; vi: lithium hexamethyldisilazide, THF, chlorotrimethylsilane, -78°; then R¹-X; vii: resolution (e.g. lipase); then DBU, MeI, DMF; viii: LiOH·xH₂O, MeOH, H₂O; ix: TFA, CH₂Cl₂; x: FmocOSu, Na₂CO₃ aq., dioxane

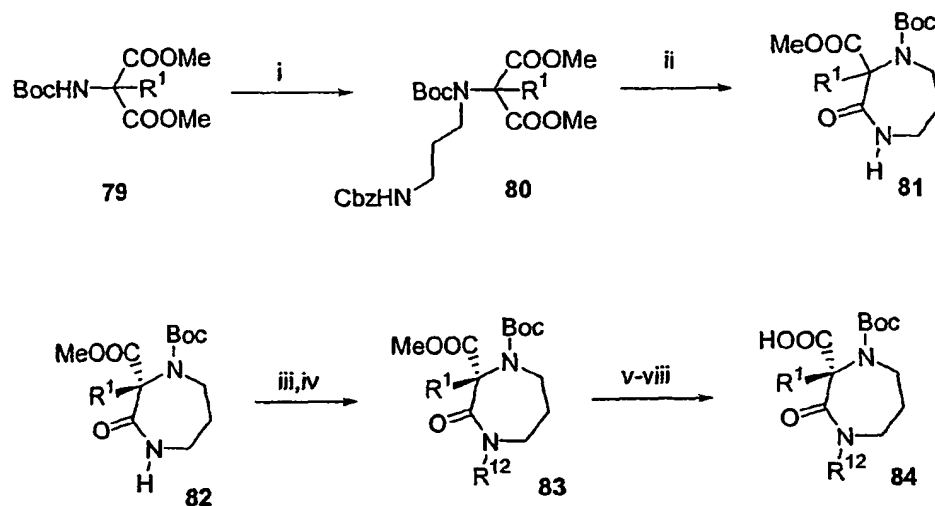
Scheme 17



i: NaN_3 , DMSO; ii: NaH, THF, $\text{CH}_2=\text{CHCOOBn}$; iii: Pd/C, H_2 , EtOH; iv: EDCI, CH_2Cl_2 , diisopropylethylamine; v: NaH, $\text{R}^{12}\text{-X}$, THF; vi: $\text{LiOH}\cdot\text{H}_2\text{O}$, MeOH, H_2O ; vii: TFA, CH_2Cl_2 ; viii: FmocOSu, $\text{Na}_2\text{CO}_3\text{aq.}$, dioxane

A55 and A56: Compounds of this type can be prepared according to *Schemes 18 and 19*.

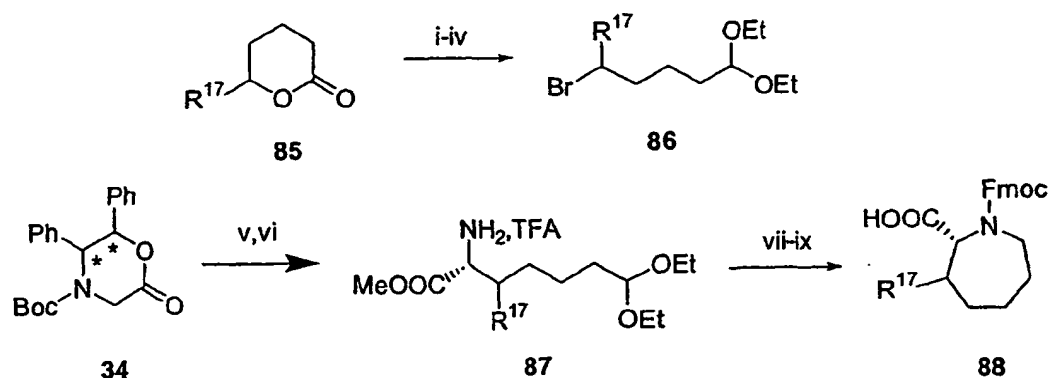
Scheme 18



i: NaH, THF, CbzNH(CH₂)₃Br; ii: Pd/C, H₂, EtOH; then toluene, heat; iii: resolution (e.g. lipase); iv: DBU, MeI, DMF; v: NaH, R¹²-X, THF; vi: LiOH·H₂O, MeOH, H₂O; vii: TFA, CH₂Cl₂; viii: FmocOSu, Na₂CO₃aq., dioxane

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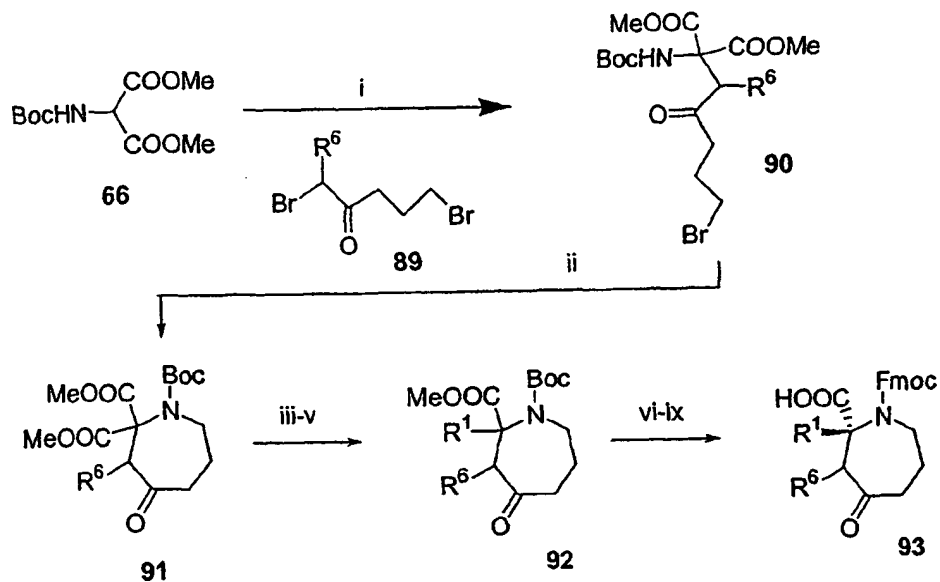
Scheme 19



i: HBr; ii: DBU, MeI, DMF; iii: DIBAL-H, THF; iv: EtOH, pyridinium p-toluenesulfonate, mol. sieves 4A; v: lithium hexamethyldisilazide, THF, -78°, 86; vi: Pd/C, H₂, EtOH; then DBU, MeI, DMF; then TFA, CH₂Cl₂; vii: HCl aq., THF; then Na(OAc)₃BH, AcOH, dichloroethane; viii: LiOH·H₂O, MeOH, H₂O; ix: FmocOSu, Na₂CO₃aq., dioxane

A57: Compounds of this type can be prepared according to Scheme 20.

5 Scheme 20

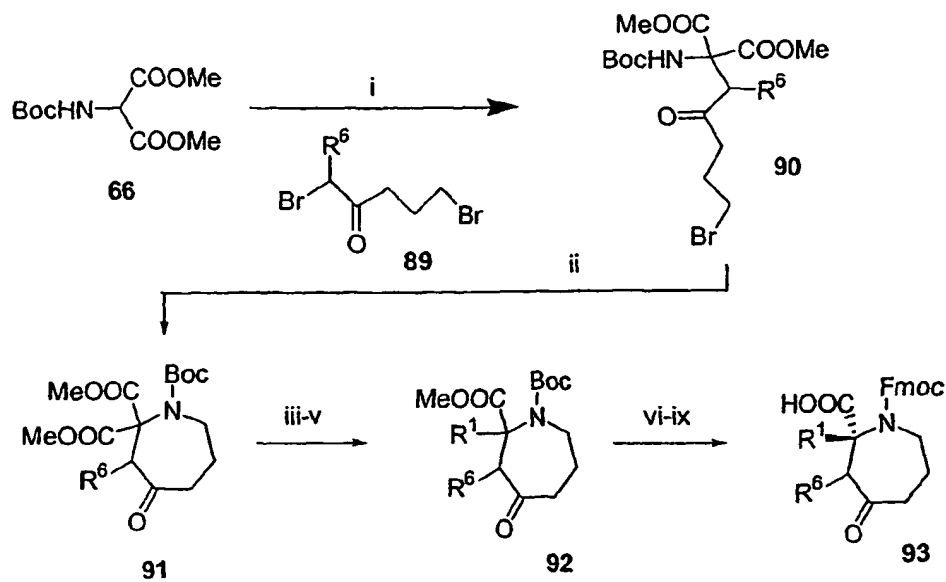


i: NaOMe, MeOH; ii: NaH, THF; iii: NaOHaq., MeOH, 75°; then HCl aq.; iv: DBU, MeI, DMF;
 v: lithium hexamethyldisilazide, THF, chlorotrimethylsilane, -78°; then R¹-X; vi: resolution (e.g.
 lipase); then isolation of methylester: DBU, MeI, DMF; vii: LiOH·H₂O, MeOH, H₂O; viii: TFA,
 CH₂Cl₂; ix: FmocOSu, Na₂CO₃ aq., dioxane

A58: See C.-H. Lee, H. Kohn, *J. Org. Chem.* 1990, 55, 6098-6104 (R¹=R⁸=H).

A59: can be prepared according to *Scheme 21*.

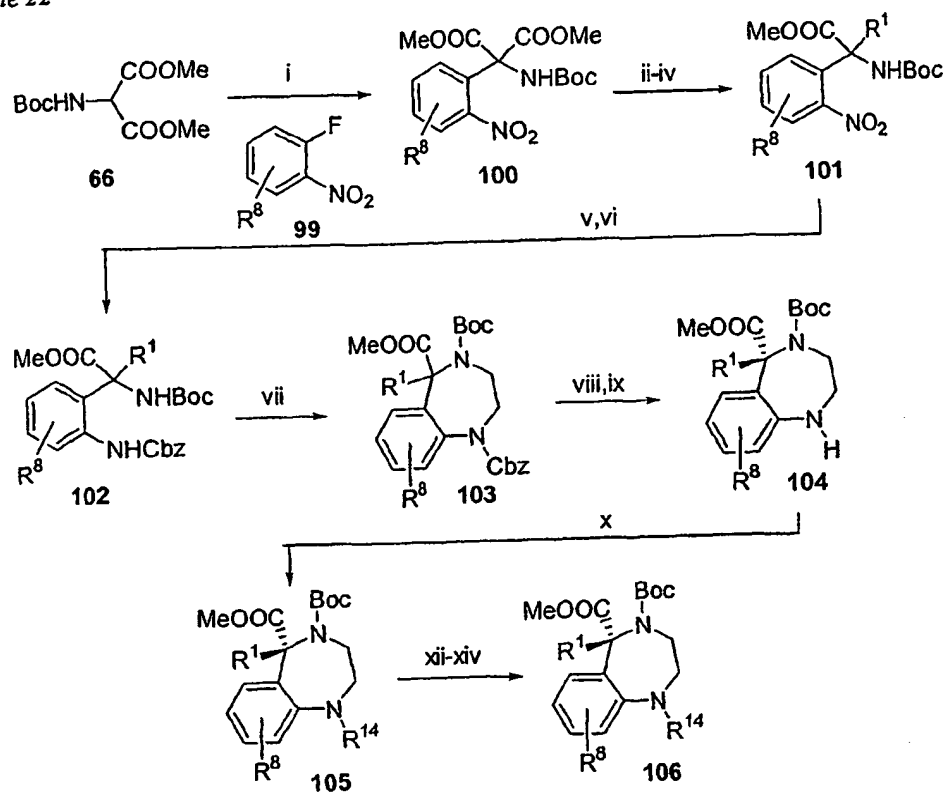
Scheme 21



i: NaOMe, MeOH; ii: NaH, THF; iii: NaOHaq., MeOH, 75°; then HCl aq.; iv: DBU, MeI, DMF;
v: lithium hexamethyldisilazide, THF, chlorotrimethylsilane, -78°; then R¹-X; vi: resolution (e.g.
lipase); then isolation of methylester. DBU, MeI, DMF; vii: LiOHx1H₂O, MeOH, H₂O; viii: TFA,
CH₂Cl₂; ix: FmocOSu, Na₂CO₃aq., dioxane

A60: Compounds of this type can be prepared according to Scheme 22.

Scheme 22



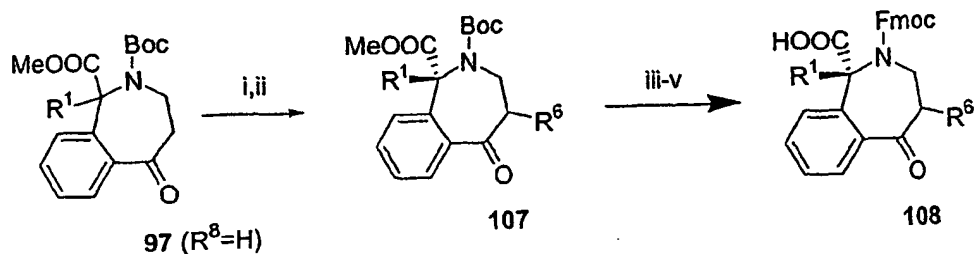
i: NaH, DMSO; ii: NaOH aq., MeOH, 75°; then HCl aq.; iii: DBU, MeI, DMF; iv: NaOMe (2.2equiv.), R¹-X; v: Raney-Ni, H₂, EtOH; vi: CbzCl, Et₃N, CH₂Cl₂; vii: NaH, Br(CH₂)₂Br, THF; viii: resolution (e.g. lipase); then DBU, MeI, DMF; ix: Pd/C, H₂, EtOH; x: NaH, R¹⁴-X, THF; xi: LiOH·1H₂O, MeOH, H₂O; xii: TFA, CH₂Cl₂; xiii: FmocOSu, Na₂CO₃ aq., dioxane

5

A61: See D. R. Armour, K. M. Morriss, M. S. Congreve, A. B. Hawcock, *Bioorg. Med. Chem. Lett.* 1997, 7, 2037-2042 (R¹=R¹²=H).

A62: Compounds of this type can be prepared according to Scheme 23.

10 Scheme 23



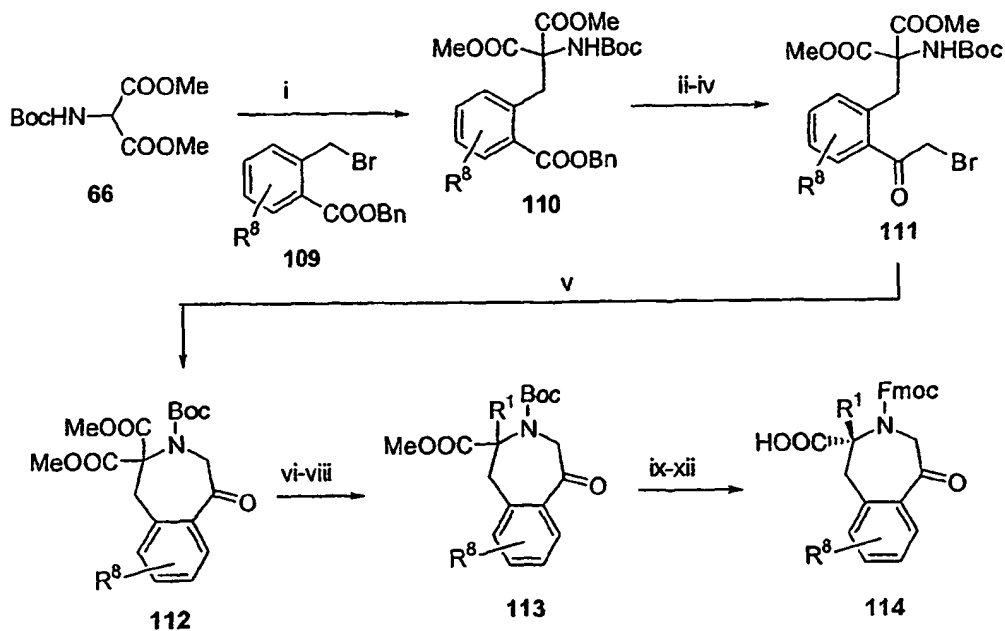
i: resolution (e.g. lipase); then DBU, MeI, DMF; ii: lithium hexamethyldisilazide, THF, chlorotrimethylsilane, -78°; then R⁶-X; iii: LiOH·1H₂O, MeOH, H₂O; iv: TFA, CH₂Cl₂; v: FmocOSu, Na₂CO₃ aq., dioxane

A63: See S. E. Gibson, N. Guillo, R. J. Middleton, A. Thuilliez, M. J. Tozer, *J. Chem. Soc. Perkin Trans. I*, 1997, 4, 447-456; S. E. Gibson, N. Guillo, S. B. Kalindjan, M. J. Tozer, *Bioorg. Med. Chem. Lett.*, 1997, 7, 1289-1292 ($R^1=H$; $R^8=H$); Beilstein Registry Number: 459155 ($R^1=H$; $R^8=4,5\text{-MeO}_2$).

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A64: Compounds of this type can be prepared according to Scheme 24.

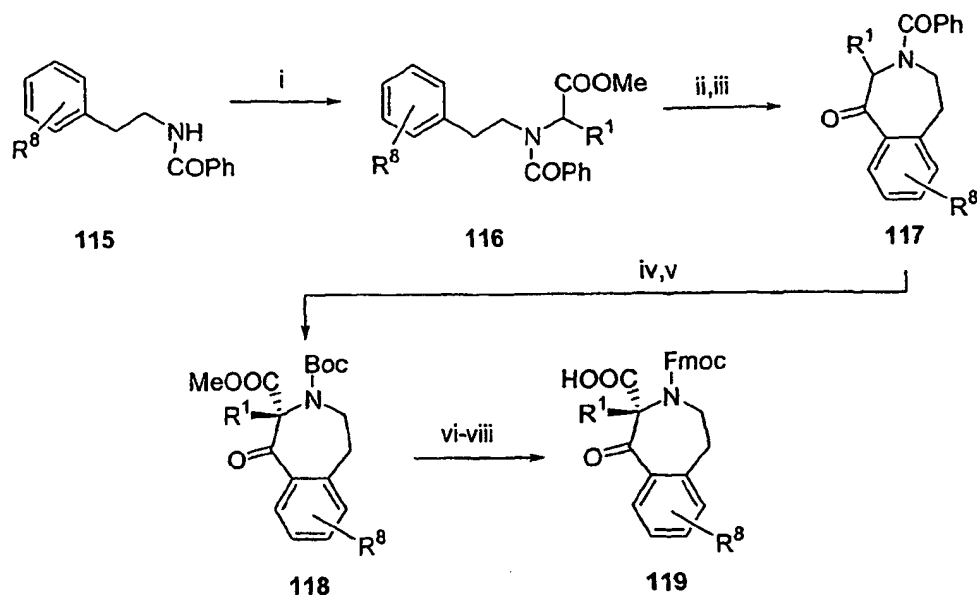
Scheme 24



i: NaH, DMSO; ii: Pd/C, H₂, EtOH; iii: iBuOCOCi, diisopropylethylamine, CH₂Cl₂; then diazomethane; iv: HBr, CH₂Cl₂; v: NaH, THF; vi: NaOHaq., MeOH, 75°; then HCl aq.; vii: DBU, MeI, DMF; viii: lithium diisopropylamide, THF, chlorotrimethylsilane, -78°; then R¹-X; ix: resolution (e.g. lipase); then isolation of methylester: DBU, MeI, DMF; x: LiOHx1H₂O, MeOH, H₂O; xi: TFA, CH₂Cl₂; xii: FmocOSu, Na₂CO₃aq., dioxane

A65 and A 67: Compounds of these types can be prepared according to *Schemes 25* and 26.

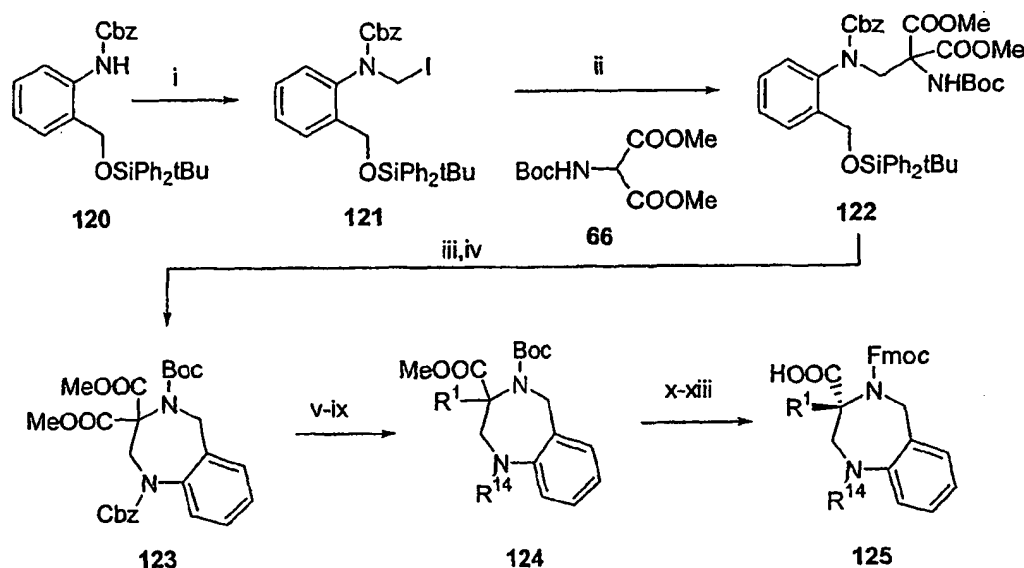
Scheme 25



i: NaH, DMSO, BrCH(R¹)COOMe; ii: LiOHx1H₂O, MeOH, H₂O; iii: polyphosphoric acid; iv: NaH, ClCOOMe, THF; v: resolution (e.g. lipase); then isolation as methylester: DBU, MeI, DMF; vi: LiOHx1H₂O, MeOH, H₂O; vii: TFA, CH₂Cl₂; viii: FmocOSu, Na₂CO₃aq., dioxane

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Scheme 26



i: NaH, THF, CH₂I₂; ii: NaH, DMSO; iii: Bu₄NF₁₀H₂O, THF; iv: methanesulfonylchloride, Et₃N, CH₂Cl₂; then NaH, THF; v: NaOH_{aq.}, MeOH, 75°; then HCl_{aq.}; vi: DBU, MeI, DMF; vii: lithium hexamethyldisilazide, THF, chlorotrimethylsilane, -78°; then R¹-X; viii: Pd/C, H₂, EtOH; ix: NaH, THF, R¹⁴-X; x: resolution (e.g. lipase); then isolation of methylester: DBU, MeI, DMF; xi: LiOHx1H₂O, MeOH, H₂O; xii: TFA, CH₂Cl₂; xiii: FmocOSu, Na₂CO₃aq., dioxane

A66: See G. L. Grunewald, L. H. Dahanukar, *J. Heterocycl. Chem.* 1994, 31, 1609-1618 ($R^1=H$; $R^8=H$, 8- NO_2 ; $C(1)=O$).

5 A68: See Griesbeck, H. Mauder, I. Müller, *Chem. Ber.* 1992, 11, 2467-2476; ($R^1=R^8=H$; $C(1)=O$).

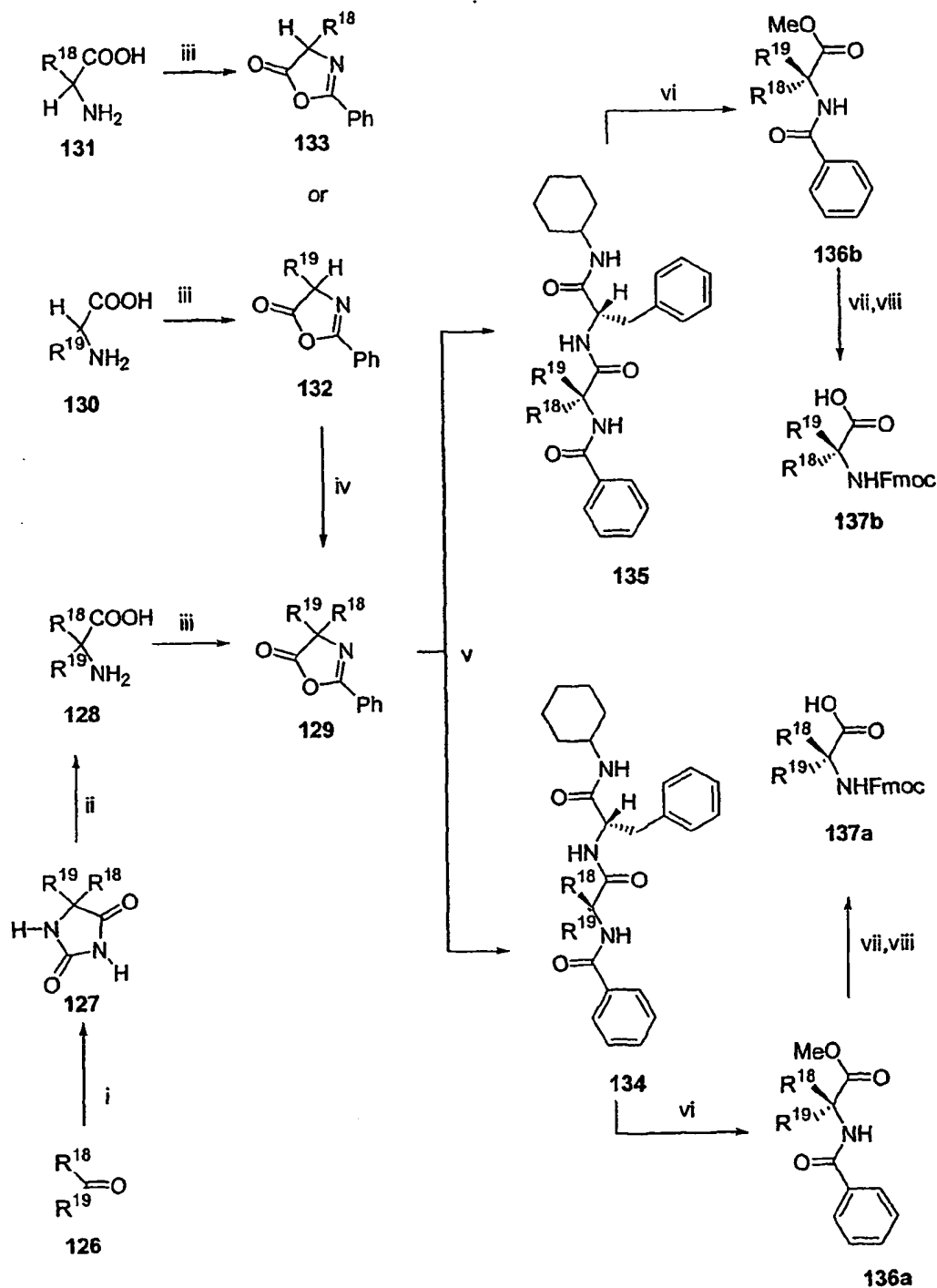
A69: R. Kreher, W. Gerhardt, *Liebigs Ann. Chem.* 1981, 240-247 ($R^1=R^8=H$).

As explained above, building blocks A70 belong to the class of open-chain α -substituted α -amino acids, A71 and A72 to the class of the the corresponding β -amino acid analogues and
10 A73-A104 to the class of the cyclic analogues of A70.

Building blocks of types A70 and A73-A104 have been synthesized by several different general methods: by [2+2] cycloaddition of ketenes with imines (I. Ojima, H. J. C. Chen, X. Quin, *Tetrahedron Lett.* 1988, 44, 5307-5318); by asymmetric aldol reaction (Y. Ito, M.
15 Sawamura, E. Shirakawa, K. Hayashikazi, T. Hayashi, *Tetrahedron Lett.* 1988, 29, 235-238; by the oxazolidinone method (J. S. Amato, L. M. Weinstock, S. Karady, US 4508921 A; M. Gander-Coquoz, D. Seebach, *Helv. Chim. Acta* 1988, 71, 224-236; A. K. Beck, D. Seebach, *Chimia* 1988, 42, 142-144; D. Seebach, J. D. Aebi, M. Gander-Coquoz, R. Naef, *Helv. Chim. Acta* 1987, 70, 1194-1216; D. Seebach, A. Fadel, *Helv. Chim. Acta* 1995, 68, 1243-1250; J.
20 D. Aebi, D. Seebach, *Helv. Chim. Acta* 1985, 68, 1507-1518; A. Fadel, J. Salaun, *Tetrahedron Lett.* 1987, 28, 2243-2246); by Schmidt- rearrangement of α,α -disubstituted α -ketoesters (G. I. Georg, X. Guan, J. Kant, *Tetrahedron Lett.* 1988, 29, 403-406); asymmetric synthesis via chiral Ni(II)- derived Schiff-bases (Y. N. Belokon, V. I. Bakhmutov, N. I. Chernoglazova, K. A. Kochetov, S. V. Vitt, N. S. Garbalinskaya, V. M. Belikov, *J. Chem.*
25 *Soc. Perkin Trans. 1*, 1988, 305-312; M. Kolb, J. Barth, *Liebigs Ann. Chem.* 1983, 1668-1688); by the bis-lactim ether synthesis (U. Schöllkopf, R. Hinrichs, R. Lonsky, *Angew. Chem.* 1987, 99, 137-138); by microbial resolution (K. Sakashita, I. Watanabe, JP 62/253397 A2) and by the hydantoin method combined with resolution of the racemic amino acids with chiral auxiliaries derived from L-phenylalanine amides (D. Obrecht, C. Spiegler, P.
30 Schönholzer, K. Müller, H. Heimgartner, F. Stierli, *Helv. Chim. Acta* 1992, 75, 1666-1696; D. Obrecht, U. Bohdal, J. Daly, C. Lehmann, P. Schönholzer, K. Müller, *Tetrahedron* 1995, 51, 10883-10900; D. Obrecht, C. Lehmann, C. Ruffieux, P. Schönholzer, K. Müller, *Helv. Chim. Acta* 1995, 78, 1567-1587; D. Obrecht, U. Bohdal, C. Broger, D. Bur, C. Lehmann, R. Ruffieux, P. Schönholzer, C. Spiegler, *Helv. Chim. Acta* 1995, 78, 563-580; D. Obrecht, H.
35 Karajiannis, C. Lehmann, P. Schönholzer, C. Spiegler, *Helv. Chim. Acta* 1995, 78, 703-714; D. Obrecht, M. Altorfer, C. Lehmann, P. Schönholzer, K. Müller, *J. Org. Chem.* 1996, 61,

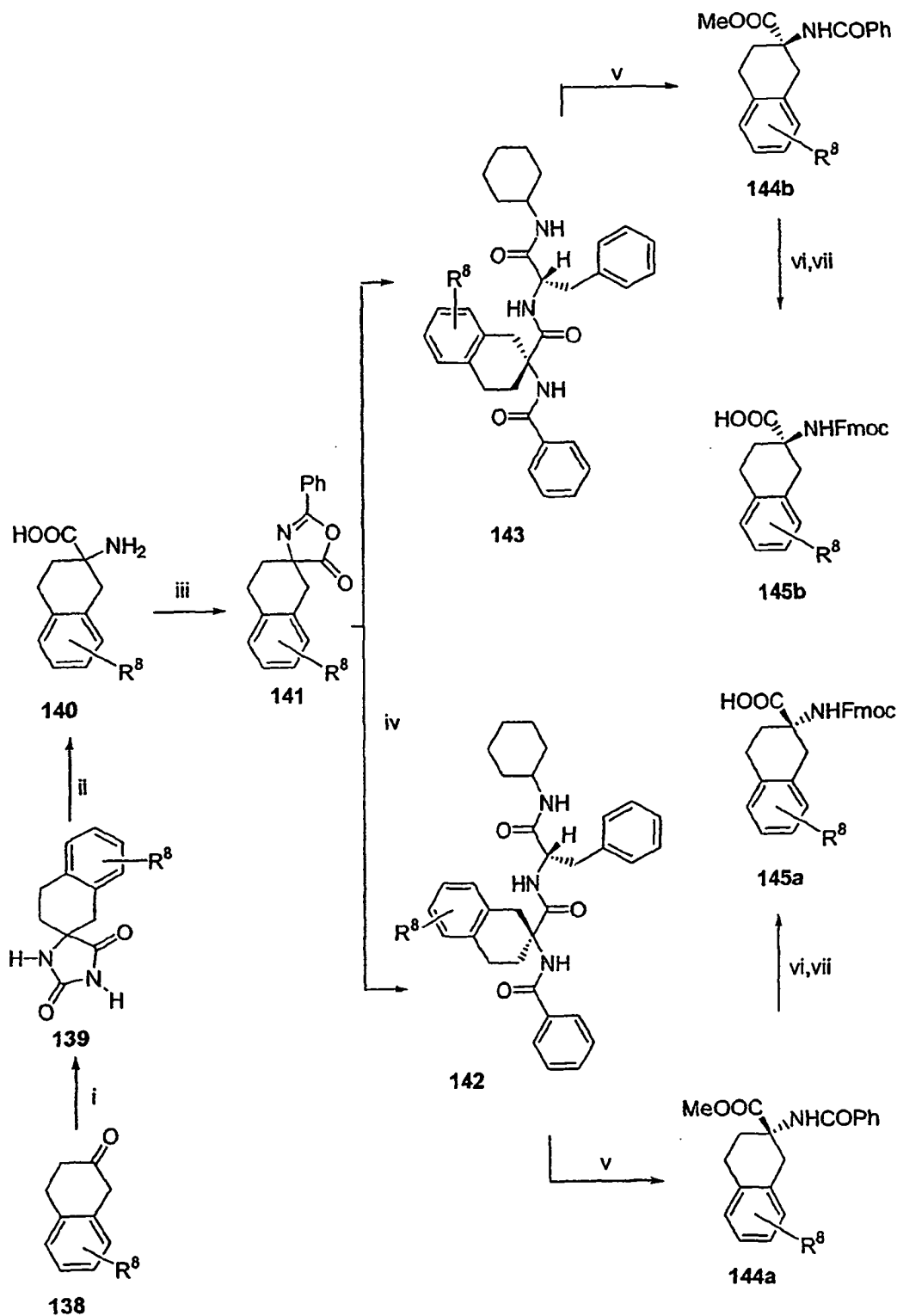
4080-4086; D. Obrecht, C. Abrecht, M. Altorfer, U. Bohdal, A. Grieder, P. Pfyffer, K. Müller, *Helv. Chim. Acta* 1996, 79, 1315-1337). The latter method has been especially useful in preparing both enantiomers of building blocks of type A70 (see Scheme 27) and A73-A104 (see Scheme 28) in pure form.

Scheme 27



- The method depicted in *Scheme 27* consists in treatment of the appropriate ketones 126 with KCN, $(\text{NH}_4)_2\text{CO}_3$ in a mixture of ethanol/water (E. Ware, *J. Chem. Res.* 1950, 46, 403; L. H. Goodson, I. L. Honigberg, J. J. Lehmann, W. H. Burton, *J. Org. Chem.* 1960, 25, 1920; S. N. Rastogi, J. S. Bindra, N. Anand, *Ind. J. Chem.* 1971, 1175) to yield the corresponding hydantoins 127, which were hydrolyzed with $\text{Ba}(\text{OH})_2$ in water at 120-140° (R. Sarges, R. C. Schur, J. L. Belletire, M. J. Paterson, *J. Med. Chem.* 1988, 31, 230) to give 128 in high yields. Schotten-Baumann acylation (Houben-Weyl, 'Methoden der Organischen Chemie', Volume XI/2, Stickstoff-Verbindungen II und III', Georg Tieme Verlag, Stuttgart, pp 339) followed by cyclization with N,N'-dicyclohexyl carbodiimide gave azlactones 129 (D. Obrecht, U. Bohdal, C. Broger, D. Bur, C. Lehmann, R. Ruffieux, P. Schönholzer, C. Spiegler, *Helv. Chim. Acta* 1995, 78, 563-580; D. Obrecht, C. Spiegler, P. Schönholzer, K. Müller, H. Heimgartner, F. Stierli, *Helv. Chim. Acta* 1992, 75, 1666-1696). Alternatively, azlactones 129 could also be prepared starting from amino acids 130 and 131, Schotten-Baumann acylation and cyclization with N,N'-dicyclohexyl carbodiimide to azlactones 132 and 133 and alkylation to yield 129 (D. Obrecht, U. Bohdal, C. Broger, D. Bur, C. Lehmann, R. Ruffieux, P. Schönholzer, C. Spiegler, *Helv. Chim. Acta* 1995, 78, 563-580; D. Obrecht, C. Spiegler, P. Schönholzer, K. Müller, H. Heimgartner, F. Stierli, *Helv. Chim. Acta* 1992, 75, 1666-1696)(see *Scheme 1*). Treatment of 129 with L-phenylalanine cyclohexylamide (D. Obrecht, U. Bohdal, C. Broger, D. Bur, C. Lehmann, R. Ruffieux, P. Schönholzer, C. Spiegler, *Helv. Chim. Acta* 1995, 78, 563-580) gave diastereomeric peptides 134 and 135, which could be conveniently separated by flash-chromatography or crystallisation. Treatment of 134 and 135 with methanesulphonic acid in methanol at 80° gave esters 136a and 136b which were converted into the corresponding Fmoc-protected final building blocks 137a and 137b.

Scheme 28

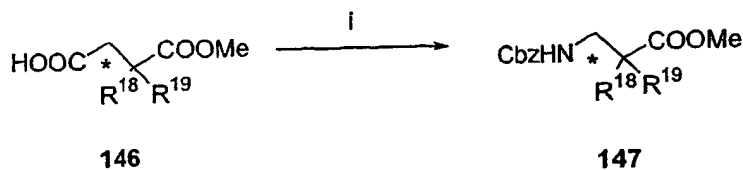


i: KCN, $(\text{NH}_4)_2\text{CO}_3$, EtOH/ H_2O ; ii: $\text{Ba}(\text{OH})_2$, H_2O ; iii: aq. NaOH, PhCOCl , dioxane; then DCC, CH_2Cl_2 ; iv: L-phenylalanine cyclohexylamide, N-methylpyrrolidone, 70° ; v: $\text{CH}_3\text{SO}_3\text{H}$, MeOH, 80° ; vi: 6N HCl aq., dioxane, 100° ; vii: Me_3SiCl , DIEA, CH_2Cl_2 ; the FmocCl

According to the general method described in *Scheme 28* (D. Obrecht, U. Bohdal, C. Broger, D. Bur, C. Lehmann, R. Ruffieux, P. Schönholzer, C. Spiegler, *Helv. Chim. Acta* 1995, 78, 563-580; D. Obrecht, C. Spiegler, P. Schönholzer, K. Müller, H. Heimgartner, F. Stierli, *Helv. Chim. Acta* 1992, 75, 1666-1696) A73-A104 can be prepared starting from the corresponding ketones 138, hydantoin formation (139) (E. Ware, *J. Chem. Res.* 1950, 46, 403; L. H. Goodson, I. L. Honigberg, J. J. Lehmann, W. H. Burton, *J. Org. Chem.* 1960, 25, 1920; S. N. Rastogi, J. S. Bindra, N. Anand, *Ind. J. Chem.* 1971, 1175; D. Obrecht, U. Bohdal, C. Broger, D. Bur, C. Lehmann, R. Ruffieux, P. Schönholzer, C. Spiegler, *Helv. Chim. Acta* 1995, 78, 563-580) and saponification ($\text{Ba}(\text{OH})_2$) to yield the racemic amino acids 140, which upon Schotten-Baumann-acylation and cyclization with $\text{N,N}'$ -dicyclohexylcarbodiimide gave azlactones 141. Reaction with L-phenylalanine cyclohexylamide (D. Obrecht, U. Bohdal, C. Broger, D. Bur, C. Lehmann, R. Ruffieux, P. Schönholzer, C. Spiegler, *Helv. Chim. Acta* 1995, 78, 563-580) gave the diastereomeric peptides 142 and 143, which were separated by flash-chromatography or crystallization. Treatment of 142 and 143 with methanesulphonic acid in methanol at 80° gave esters 144a and 144b which were converted into the corresponding suitably protected amino acid precursors 145a and 145b, ready for peptide synthesis.

A71: Amino acid building blocks of this type (see formula 147) can be conveniently prepared from the corresponding disubstituted succinates 146 by *Curtius-rearrangement* as shown in *Scheme 29*.

Scheme 29



i: diphenylphosphoryl azide, toluene, 80° ; then benzyl alcohol

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A71: See D. Seebach, S. Abele, T. Sifferlen, M. Haenggi, S. Gruner, P. Seiler, *Helv. Chim. Acta* 1998, 81, 2218-2243 (R^{18} and R^{19} form: $-(\text{CH}_2)_2-$; $-(\text{CH}_2)_3-$; $-(\text{CH}_2)_4-$; $-(\text{CH}_2)_5-$; $\text{R}^{20}=\text{H}$); L. Ducrie, S. Reinelt, P. Seiler, F. Diederich, D. R. Bolin, R. M. Campbell, G. L. Olson, *Helv. Chim. Acta* 1999, 82, 2432-2447; C. N. C. Drey, R. J. Ridge, *J. Chem. Soc. Perkin Trans.1*, 1981, 2468-2471; U. P. Dhokte, V. V. Khau, D. R. Hutchinson, M. J. Martinelli, *Tetrahedron Lett.* 1998, 39, 8771-8774 ($\text{R}^{18}=\text{R}^{19}=\text{Me}$; $\text{R}^{20}=\text{H}$); D. L. Varie, D. A. Hay, S. L. Andis, T. H. Corbett, *Bioorg. Med. Chem. Lett.* 1999, 9, 369-374 ($\text{R}^{18}=\text{R}^{19}=\text{Et}$); Testa, *J. Org. Chem.*

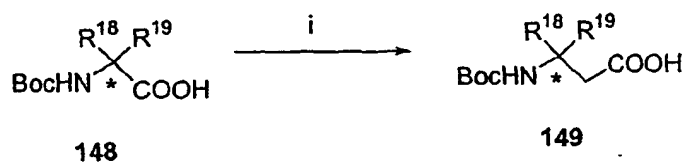
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1959, 24, 1928-1936 ($R^{18} = \text{Et}$; $R^{19} = \text{Ph}$); M. Haddad, C. Wakselman, *J. Fluorine Chem.* 1995, 73, 57-60 ($R^{18} = \text{Me}$; $R^{19} = \text{CF}_3$; $R^{20} = \text{H}$); T. Shono, K. Tsubata, N. Okinaga, *J. Org. Chem.* 1984, 49, 1056-1059 ($R^{18} = R^{19} = R^{20} = \text{Me}$); K. Ikeda, Y. Terao, M. Sekiya, *Chem. Pharm. Bull.* 1981, 29, 1747-1749 (R^{18} and R^{19} form: $-(\text{CH}_2)_5-$; $R^{20} = \text{Me}$).

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Amino acid building blocks of type A72 can be conveniently prepared by *Arndt-Eistert* C1-homologation of compounds of type A70 according to *Scheme 30*.

Scheme 30



10 i: $i\text{BuOCOCl}$, diisopropylethylamine, CH_2Cl_2 ; then diazomethane, $h\nu$ or Cu(I)

A72: See Y. V. Zeifman, *J. Gen. Chem. USSR* (Engl. Trans.) 1967, 37, 2355-2363 ($R^{18} = R^{19} = \text{CF}_3$); W. R. Schoen, J. M. Pisano, K. Pendergast, M. J. Wyvratt, M. H. Fisher, *J. Med. Chem.* 1994, 37, 897-906; S. Thaisrivongs, D. T. Pals, D. W. DuCharme, S. Turner, G. L. DeGraaf, *J. Med. Chem.* 1991, 34, 655-642; T. K. Hansen, H. Thøgersen, B. S. Hansen, *Bioorg. Med. Chem. Lett.* 1997, 7, 2951-2954; R. J. DeVita, R. Bochis, A. J. Frontier, A. Kotliar, M. H. Fisher, *J. Med. Chem.* 1998, 41, 1716-1728; D. Seebach, P. E. Ciceri, M. Overhand, B. Jaun, D. Rigo, *Helv. Chim. Acta* 1996, 79, 2043-2066; R. P. Nargund, K. H. Barakat, K. Cheng, W. Chan, B. R. Butler, A. A. Patchett, *Bioorg. Med. Chem. Lett.* 1996, 6, 1265-1270 ($R^{18} = R^{19} = \text{Me}$); E. Altmann, K. Nebel, M. Mutter, *Helv. Chim. Acta* 1991, 74, 800-806 ($R^{18} = \text{Me}$; $R^{19} = \text{COOMe}$).

A73: Compounds of this type can be prepared according to C. Mapelli, G. Taroccy, F. Schwitzer, C. H. Stammer, *J. Org. Chem.* 1989, 54, 145-149 ($R^{21} = 4\text{-OHC}_6\text{H}_4$); F. Elrod, E. M. Holt, C. Mapelli, C. H. Stammer, *J. Chem. Soc. Chem. Commun.* 1988, 252-253 ($R^{21} = \text{CH}_2\text{COOMe}$); R. E. Mitchell, M. C. Pirrung, G. M. McGeehan, *Phytochemistry* 1987, 26, 2695 ($R^{21} = \text{CH}_2\text{OH}$); J. Bland, A. Batolussi, C. H. Stammer, *J. Org. Chem.* 1988, 53, 992-995 ($R^{21} = \text{CH}_2\text{NH}_2$). Additional derivatives of A73 have been described by T. Wakamiya, Y. Oda, H. Fujita, T. Shiba, *Tetrahedron Lett.* 1986, 27, 2143-2134; U. Schöllkopf, B. Hupfeld, R. Gull, *Angew. Chem.* 1986, 98, 755-756; J. E. Baldwin, R. M. Adlington, B. J. Rawlings, *Tetrahedron Lett.* 1985, 26, 481-484; D. Kalvin, K. Ramalinggam, R. Woodard, *Synth. Comm.* 1985, 15, 267-272 and L. M. Izquierdo, I. Arenal, M. Bernabe, E. Alvarez, *Tetrahedron Lett.* 1985, 41, 215-220.

A74: Compounds of this type can be prepared according to general method described in *Scheme 28* starting from the corresponding cyclobutanones.

- 5 A75 and A76: Compounds of this type can be prepared using the following methods: P. Hughes, J. Clardy, *J. Org. Chem.* 1988, 53, 4793-4796; E. A. Bell, M. Y. Qureshi, R. J. Pryce, D. H. Janzen, P. Lemke, J. Clardy, *J. Am. Chem. Soc.* 1980, 102, 1409; Y. Gaoni, *Tetrahedron Lett.* 1988, 29, 1591-1594; R. D. Allan, J. R. Haurahan, T. W. Hambley, G. A. R. Johnston, K. N. Mewett, A. D. Mitrovic, *J. Med. Chem.* 1990, 33, 2905-2915 ($R^{23} =$
10 $COOH$); G. W. Fleet, J. A. Seijas, M. Vasquez Tato, *Tetrahedron* 1988, 44, 2077-2080 ($R^{23} =$
 CH_2OH).

A77: Compounds of this type can be prepared according to J. H. Burekhalter, G. Schmied, *J. Pharm. Sci.* 1966, 55, 443-445 ($R^{23} = \text{aryl}$).

15

A78: Compounds of this type can be prepared according to J. C. Watkins, P. Kroosgard-Larsen, T. Honoré, *TIPS* 1990, 11, 25-33; F. Trigalo, D. Brisson, R. Azerad, *Tetrahedron Lett.* 1988, 29, 6109 ($R^{24} = COOH$).

- 20 A79: Compounds of this type can be prepared according to general method described in *Scheme 28* starting from the corresponding pyrrolidine-3-ones.

A80-A82: Compounds of this type can be prepared according to D. M. Walker, E. W. Logusch, *Tetrahedron Lett.* 1989, 30, 1181-1184; Y. Morimoto, K. Achiwa, *Chem. Pharm. Bull.* 1989, 35, 3845-3849; J. Yoshimura, S. Kondo, M. Ihara, H. Hashimoto, *Carbohydrate Res.* 1982, 99, 129-142.

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A83: Compounds of this type can be prepared according to general method described in *Scheme 28* starting from the corresponding pyrazoline-4-ones.

30

A84: Compounds of this type can be prepared according to R. M. Pinder, B. H. Butcher, D. H. Buxton, D. J. Howells, *J. Med. Chem.* 1971, 14, 892-893; D. Obrecht, U. Bohdal, C. Broger, D. Bur, C. Lehmann, R. Ruffieux, P. Schönholzer, C. Spiegler, *Helv. Chim. Acta* 1995, 78, 563-580.

35

A85: Compounds of this type can be prepared according to general method described in *Scheme 28* starting from the corresponding indane-1,3-diones.

- A86: Compounds of this type can be prepared according to general method described in *Scheme 28* starting from the corresponding indane-2-ones.
- 5 A87: Compounds of this type and analogues thereof can be prepared according to C. Cativiela, M. D. Diaz de Villegas, A. Avenoza, J. M. Peregrina, *Tetrahedron* **1993**, *47*, 10987-10996; C. Cativiela, P. Lopez, J. A. Mayoral, *Tetrahedron Asymmetry* **1990**, *1*, 379; C. Cativiela, J. A. Mayoral, A. Avenoza, M. Gonzalez, M. A. Rey, *Synthesis* **1990**, 1114.
- 10 A87 and A88: Compounds of this type can be prepared according to L. Munday, *J. Chem. Soc.* **1961**, 4372; J. Ansell, D. Morgan, H. C. Price, *Tetrahedron Lett.* **1978**, *47*, 4615-4616.
- A89: Compounds of this type can be prepared according to general method described in *Scheme 28* starting from the corresponding piperidine-3-ones.
- 15 A90: Compounds of this type can be prepared according to general method described in *Scheme 28* starting from the corresponding tetrahydrothiapyran-3-ones.
- A91: Compounds of this type can be prepared according to general method described in
- 20 *Scheme 28* starting from the corresponding tetrahydropyran-3-ones.
- A92: Compounds of this type can be prepared according to general method described in *Scheme 28* starting from the corresponding piperidine-2,5-diones.
- 25 A93: Compounds of this type can be prepared according to general method described in *Scheme 28* starting from the corresponding cyclohexanones.
- A94: Compounds of this type can be prepared according to *J. Org. Chem.* **1990**, *55*, 4208.
- 30 A95: Compounds of this type can be prepared according to N. J. Lewis, R. L. Inloes, J. Hes, R. H. Matthews, G. Milo, *J. Med. Chem.* **1978**, *21*, 1070-1073.
- A96: Compounds of this type can be prepared according to general method described in *Scheme 28* starting from the corresponding tetrahydropyran-4-ones.
- 35 A97: Compounds of this type can be prepared according to general method described in *Scheme 28* starting from the corresponding piperidine-2,4-diones.

A98: Compounds of this type can be prepared according to general method described in *Scheme 28* starting from the corresponding 1-tetralones (D. Obrecht, C. Spiegler, P. Schönholzer, K. Müller, H. Heimgartner, F. Stierli, *Helv. Chim. Acta* 1992, 75, 1666-1696).

5

A99: Compounds of this type can be prepared according to general method described in *Scheme 28* starting from the corresponding tetraline-1,4-dione mono-diethylacetals.

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A100: Compounds of this type can be prepared according to general method described in *Scheme 28* starting from the corresponding tetrahydroquinolin-4-ones.

A101: Compounds of this type can be prepared according to general method described in *Scheme 28* starting from the corresponding tetrahydroquinoline-2,4-diones.

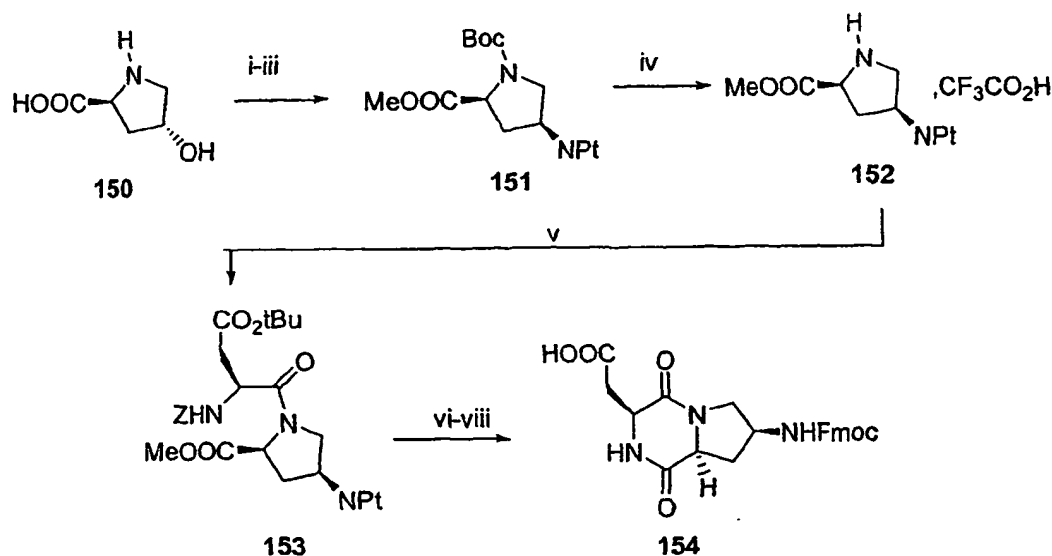
- 15 A102: Compounds of this type can be prepared according to K. Ishizumi, N. Ohashi, N. Tanno, *J. Org. Chem.* 1987, 52, 4477-4485; D. Obrecht, U. Bohdal, C. Broger, D. Bur, C. Lehmann, R. Ruffieux, P. Schönholzer, C. Spiegler, *Helv. Chim. Acta* 1995, 78, 563-580; D. Obrecht, C. Spiegler, P. Schönholzer, K. Müller, H. Heimgartner, F. Stierli, *Helv. Chim. Acta* 1992, 75, 1666-1696; D. R. Haines, R. W. Fuller, S. Ahmad, D. T. Vistica, V. E. Marquez, *J. Med. Chem.* 1987, 30, 542-547; T. Decks, P. A. Crooks, R. D. Waigh, *J. Pharm. Sci* 1984, 73, 457-460; I. A. Blair, L. N. Mander, *Austr. J. Chem.* 1979, 32, 1055-1065.

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Overviews dealing with building blocks of types (b)-(p) are: S. Hanessian, G. McNaughton-Smith, H.-G. Lombart, W. D. Lubell, *Tetrahedron* 1997, 38, 12789-12854; D. Obrecht, M. Altorfer, J. A. Robinson, "Novel Peptide Mimetic Building Blocks and Strategies for Efficient Lead Finding", *Adv. Med. Chem.* 1999, Vol.4, 1-68

Templates of type (b1) can be prepared according to *Schemes 31* and *32*.

Scheme 31



5

- i: Treatment of 150 with a dehydrating reagent such as thionylchloride in methanol at an elevated temperature, conveniently at reflux.
- ii: Introduction of Boc, e.g. using di-tert.-butyl dicarbonate and triethylamine in a suitable solvent such as dichloromethane; any other suitable N-protecting group (not shown in Reaction Scheme 31) can be introduced in an analogous manner.
- iii: Reaction of formed product with phthalimide, diethyl diazodicarboxylate and triphenylphosphine under standard Mitsunobu conditions (Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* 1972, 94, 672) to conveniently yield 151.
- iv: Treatment of 151 with trifluoroacetic acid in dichloromethane.
- v: 152 is coupled under standard peptide coupling conditions with Cbz-Asp(tBu)OH in DMF with reagents such as HBTU and 1-hydroxybenztriazole (HOBt) with a base such as diisopropylethylamine to yield 153.
- vi: Removal of the Cbz-group, conveniently by hydrogenation using H₂ and a catalyst such as Palladium on charcoal, in solvents such as ethanol, DMF and ethyl acetate.
- vii: The phthalimide group is cleaved off from the resulting product, conveniently by treatment with hydrazine in a suitable solvent such as ethanol at an elevated temperature, suitably at about 80° C and cleavage of the formed product with trifluoroacetic acid in CH₂Cl₂.
- viii: The formed amino acid is conveniently protected with reagents such as 9-fluorenylmethoxycarbonyl chloride or 9-fluorenylmethoxycarbonyl succinimide using a

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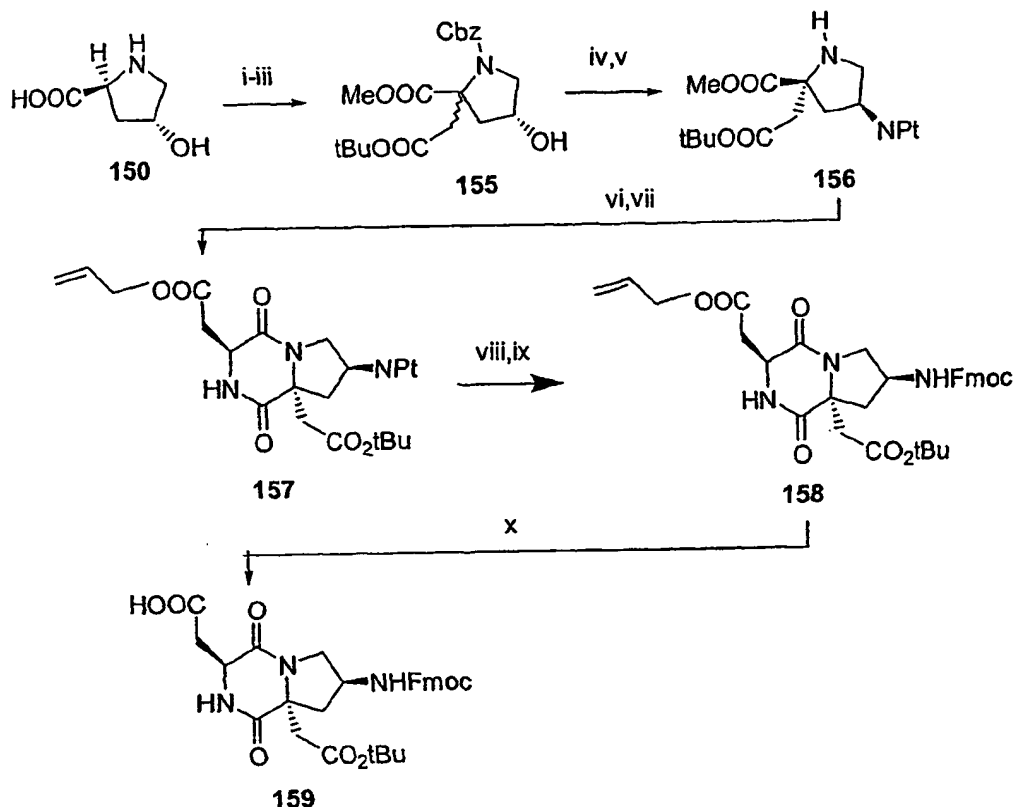
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base such as sodium carbonate or triethylamine in a suitable solvent or mixture of solvents such as dioxane and water, or dichloromethane to yield **154** as described by Bisang, C.; Weber, C.; Robinson, J. A. *Helv. Chim. Acta* 1996, 79, 1825-1842.

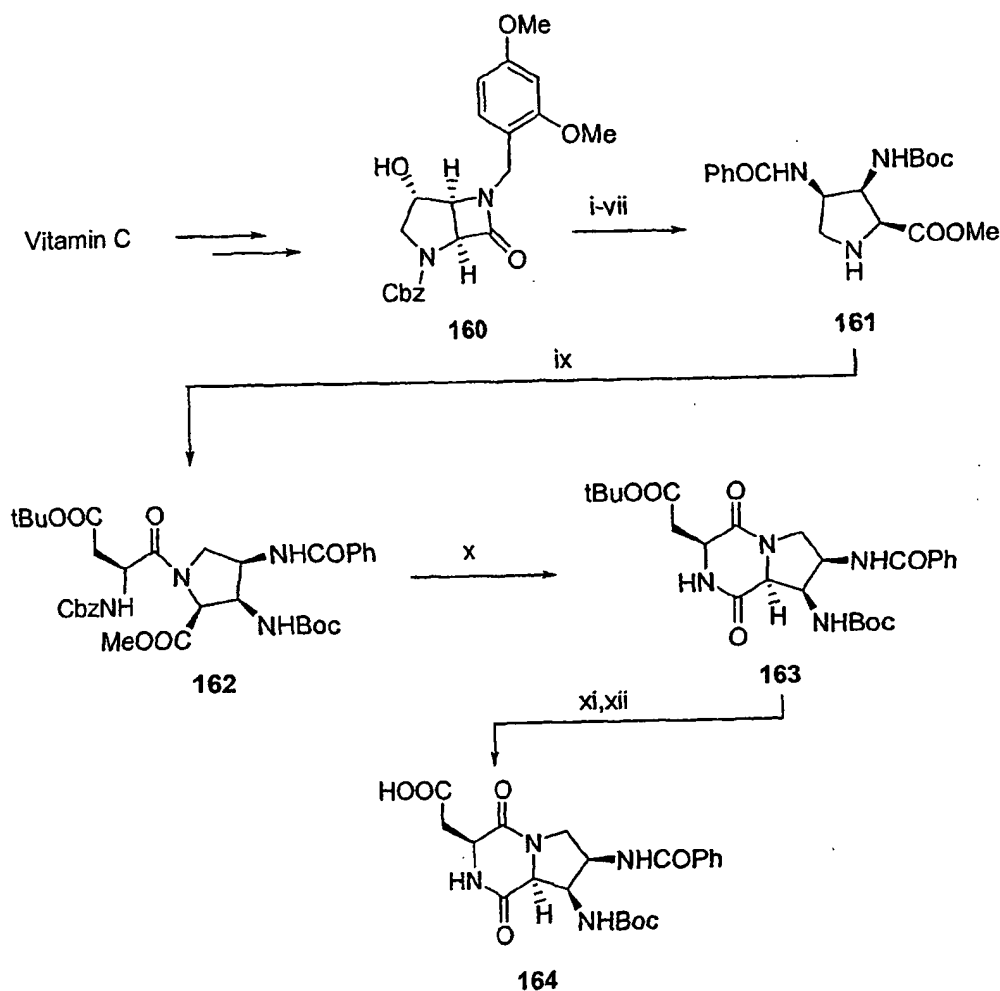
5 *Scheme 32*



- i: Treatment of **150** with a dehydrating reagent such as thionyl chloride in a suitable solvent such as methanol at an elevated temperature, conveniently at reflux.
- ii: The resulting amino acid ester is N-protected under standard conditions for introducing the Cbz-group, e.g. using benzyloxycarbonyl chloride and triethylamine in a suitable solvent such as dichloromethane.
- 10 iii: The Cbz-protected amino acid methyl ester is treated with trimethylsilylchloride and a base such as triethylamine in a solvent such as tetrahydrofuran, cooled, conveniently to about -78°C , followed by reaction with a strong base such as lithium diisopropylamide or lithium hexamethyldisilylazide and tert.-butyl bromoacetate yielding **155** as a mixture of diastereomers as described by Bisang, C.; Jiang, L.; Freund, E.; Emery, F.; Bauch, C.; Matile, H.; Pluschke, G.; Robinson, J. A. *J. Am. Chem. Soc.* 1998, 120, 7439-7449; Emery, F.; Bisang, C.; Favre, M.; Jiang, L.; Robinson, J. A. *J. Chem. Soc. Chem. Commun.* 1996, 2155-2156.
- 15

- iv: Reaction of 155 with phthalimide, diethyl diazodicarboxylate and triphenylphosphine under standard Mitsunobu conditions (Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* 1972, 94, 672).
- 5 v: The resulting product is hydrogenated using H₂ and a suitable catalyst such as palladium on charcoal in a solvent such as ethyl acetate, DMF or ethanol; subsequently separation of diastereomers takes place and yields 156.
- vi: 156 is coupled with Fmoc-Asp(allyl)OH under standard peptide coupling conditions using reagents such as HATU, HOAt and a base such as diisopropylethylamine in a suitable solvent such as DMF.
- 10 vii: Cyclization, conveniently with DBU in DMF to yield 157.
- viii: The phthalimide group is cleaved off from resulting product, conveniently by hydrazinolysis, e.g. treatment with methylhydrazine in a suitable solvent such as DMF.
- ix: The formed product is conveniently protected with reagents such as 9-15 fluorenylmethoxycarbonyl chloride or 9-fluorenylmethoxycarbonyl succinimide using a base such as sodium carbonate or triethylamine in a suitable solvent or mixture of solvents such as dioxane and water, or dichloromethane to yield 158.
- x: Standard removal of an allyl ester group using e.g. palladium(0) as catalyst gives 159.
- 20 Templates of type (b2) can be prepared according to Scheme 33.

Scheme 33

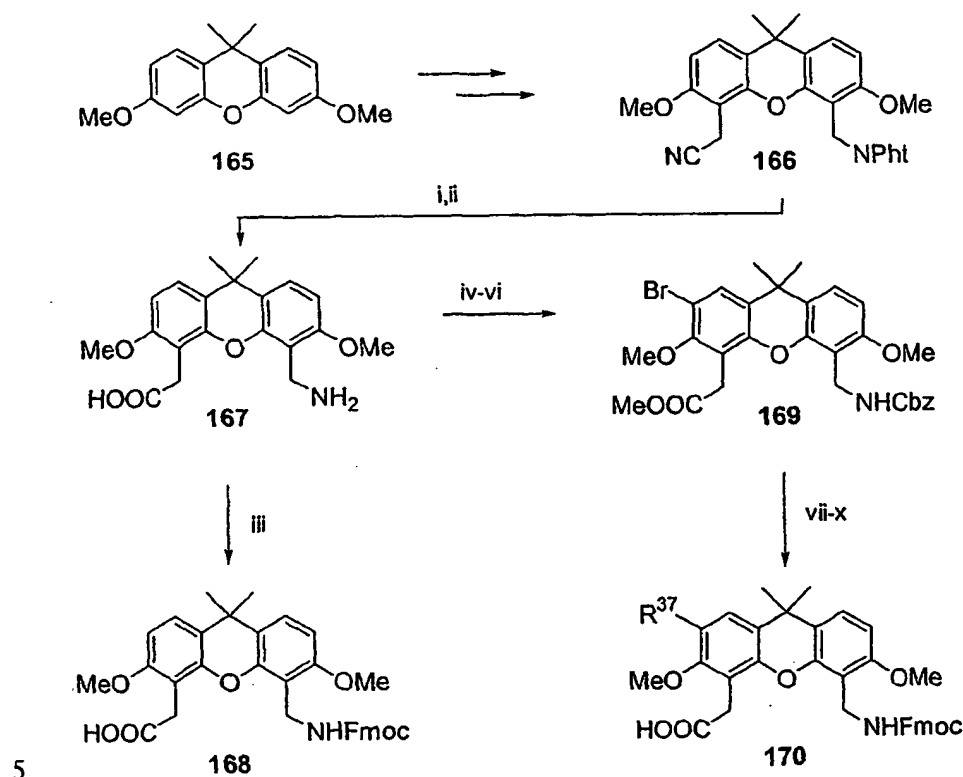


- 5 i: 160 (obtainable from Vitamin C as described by Hubschwerlen, C. (*Synthesis* 1986, 962) is treated with phthalimide, diethyl diazodicarboxylate and triphenylphosphine under standard Mitsunobu conditions (Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* 1972, 94, 672).
- 10 ii: The phthalimide group is cleaved off from the product, conveniently by hydrazinolysis, e.g. by treatment with methylhydrazine in a suitable solvent such as DMF.
- iii: The amino group is protected by treatment with a benzoylating reagent such as benzoic acid anhydride or benzoylchloride and a base such as triethylamine or 4-dimethylaminopyridine in a suitable solvent such as dichloromethane or DMF.
- 15 iv: Removal of the 2,4-dimethoxybenzyl group, e.g. with $\text{K}_2\text{S}_2\text{O}_8$ and Na_2HPO_4 in aqueous acetonitrile at an elevated temperature, e.g. at about 80° C.

- v: Introduction of a tert.-butoxycarbonyl group using e.g. di-tert.-butyloxycarbonyl dicarbonate, triethylamine and a catalytic amount of 4-dimethylaminopyridine in a suitable solvent such as dichloromethane.
- vi: Reaction with aqueous sodium carbonate in tetrahydrofuran followed by acidification.
- 5 vii: Esterification of the carboxylic acid group, conveniently with diazomethane in a suitable solvent such as diethylether yielding 161.
- viii Removal of the Cbz-group, conveniently by hydrogenation with H₂ in the presence of a catalyst such as palladium on charcoal in a solvent such as DMF to yield 161 as described by Pfeifer, M.; Robinson, J. A. *J. Chem. Soc. Chem. Commun.* 1998, 1977.
- 10 ix: 161 is coupled under standard peptide coupling conditions with Cbz-Asp(tBu)OH in DMF with reagents such as HBTU and 1-hydroxybenztriazole with a base such as diisopropylethylamine to yield 162 as described by Pfeifer, M.; Robinson, J. A. *J. Chem. Soc. Chem. Commun.* 1998, 1977.
- x: Removal of the Cbz-group, e.g. by hydrogenation using H₂ and a catalyst such as palladium on charcoal under standard conditions, yields 163 as described by Pfeifer, M.; Robinson, J. A. *J. Chem. Soc. Chem. Commun.* 1998, 1977.
- 15 xi: Cleavage of the tert.-butyl ester and tert.-butyloxycarbonyl groups, conveniently using trifluoroacetic acid in dichloromethane or 4N hydrochloric acid in dioxane.
- xii: The intermediate free amino acid formed is conveniently protected with reagents such as 9-fluorenylmethoxycarbonyl chloride or 9-fluorenylmethoxycarbonyl succinimide using a base such as sodium carbonate or triethylamine in a suitable solvent or mixture of solvents such as dioxane and water, or dichloromethane to yield 164 as described by Pfeifer, M.; Robinson, J. A. *J. Chem. Soc. Chem. Commun.* 1998, 1977.
- 20

Templates of type (c1) can be prepared according to *Schemes 34 to 37*.

Scheme 34

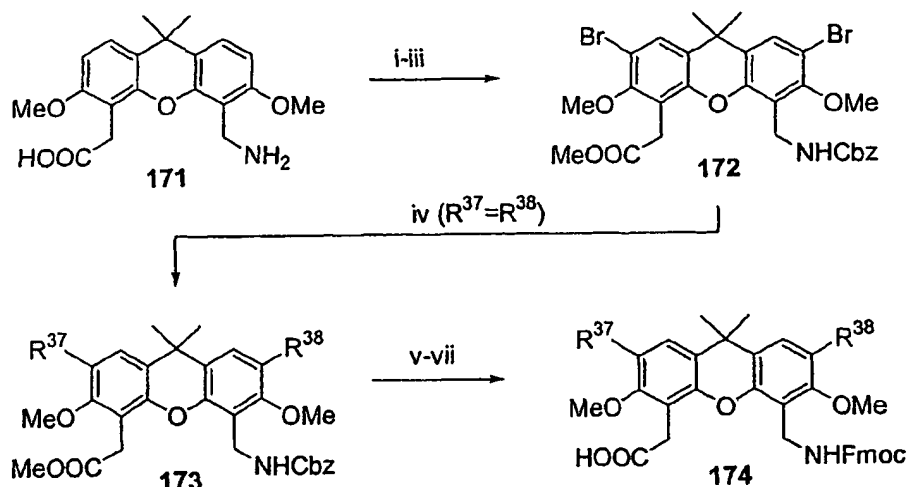


- i: 166 can be synthesized from 165 according to P. Waldmeier, "Solid-supported synthesis of highly substituted xanthene-derived templates for the synthesis of β -turn stabilized cyclic peptide libraries", PhD-thesis, University of Zurich, 1996. For cleaving the phthalimide group 166 is conveniently submitted to hydrazinolysis, e.g. by treatment with hydrazine hydrate in a suitable solvent such as ethanol at an elevated temperature, e.g. at about 80° C.
- ii: The intermediate aminonitrile is saponified, conveniently under basic conditions, e.g. with aqueous sodium hydroxide in a suitable solvent such as ethanol at an elevated temperature, conveniently under reflux, to yield 167.
- iii: The intermediate free amino acid formed is conveniently protected with reagents such as 9-fluorenylmethoxycarbonyl chloride or 9-fluorenylmethoxycarbonyl succinimide using a base such as sodium carbonate or triethylamine in a suitable solvent or mixture of solvents such as dioxane and water, or dichloromethane to yield 168 as described by P. Waldmeier, "Solid-supported synthesis of highly substituted

xanthene-derived templates for the synthesis of β -turn stabilized cyclic peptide libraries", PhD-thesis, University of Zurich, 1996.

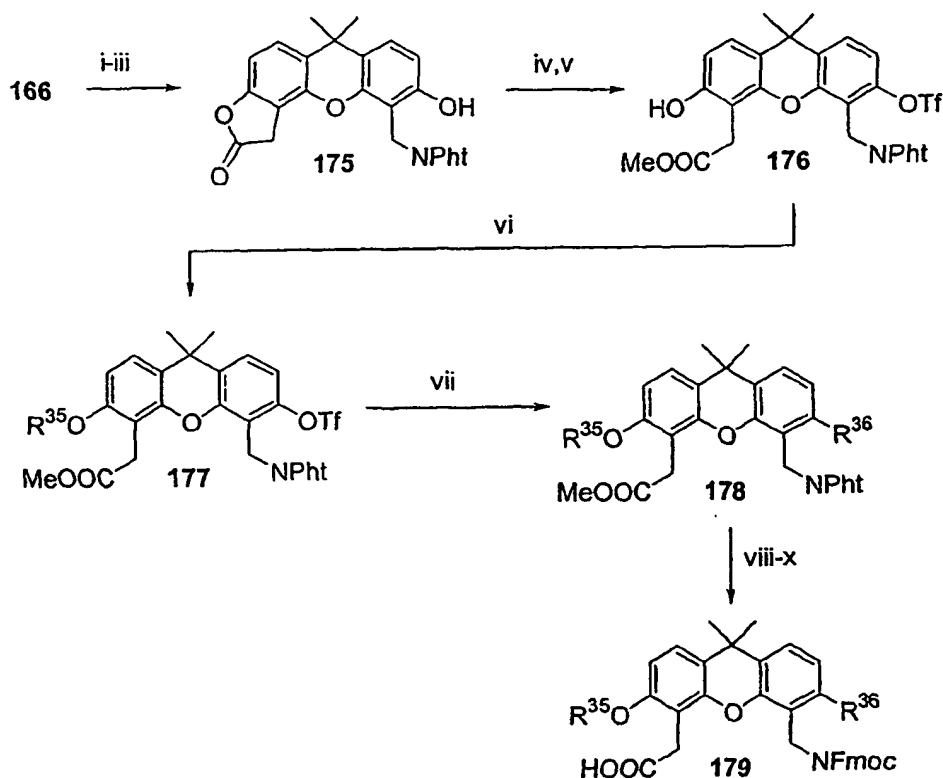
- iv: Regioselective bromination of 167 is performed preferably with bromine in acetic acid and dichloromethane. In a similar fashion $R^{37} = NO_2$ can be introduced by treatment with HNO_3 in acetic acid and $R^{37} = CH_2-NPh$ by treatment with hydroxymethyl phthalimide in H_2SO_4 .
- v: The amino group is conveniently Cbz-protected with reagents such as benzyloxycarbonyl chloride or succinimide in a suitable solvent such as dioxane in presence of a base such as aqueous sodium hydroxide.
- 10 vi: The carboxylic acid group is esterified, preferably with DBU and methyl iodide in DMF to yield 169.
- vii: Introduction of lower alkyl, substituted lower alkyl and aryl substituents (R^{37}), conveniently by palladium(0)-catalyzed Stille- (Stille, J.K. *Angew. Chem.* 1986, 68, 504) and Suzuki- couplings (Oh-e, T.; Mijaura, N.; Suzuki, A. *J. Org. Chem.* 1993, 58, 2201). Any other functionalization known for aryl bromides can be employed for introduction of substituents R^{37} .
- 15 viii: Removal of the Cbz-group, e.g. by hydrogenation using H_2 and a catalyst such as palladium on charcoal in a suitable solvent such as ethanol, DMF and ethyl acetate.
- ix: Hydrolysis of the ester group, conveniently under acidic conditions, e.g. with 25% aqueous hydrochloric acid in a suitable solvent such as dioxane at an elevated temperature, preferably at about 100° C.
- 20 x: The intermediate free amino acid formed is conveniently protected with reagents such as 9-fluorenylmethoxycarbonyl chloride or 9-fluorenylmethoxycarbonyl succinimide using a base such as sodium carbonate or triethylamine in a suitable solvent or mixture of solvents such as dioxane and water, or dichloromethane to yield 170.
- 25

Scheme 35



- 5 i: Double ortho- bromination of 171 is performed preferably with excess bromine in acetic acid and dichloromethane. In a similar fashion $R^{37} = R^{38} = NO_2$ can be introduced by treatment with HNO_3 in acetic acid and $R^{37} = R^{38} = CH_2-NPh$ by treatment with hydroxymethyl phthalimide in H_2SO_4 .
- 10 ii: The amino group is protected, conveniently Cbz-protected, with reagents such as benzyloxycarbonyl chloride or succinimide in a suitable solvent such as dioxane in the presence of a base such as aqueous sodium hydroxide.
- iii: The carboxylic acid group is esterified, preferably with DBU and methyl iodide in DMF to yield 172.
- 15 iv: Introduction of lower alkyl, substituted lower alkyl and aryl substituents ($R^{37} = R^{38}$), e.g. by palladium(0)- catalyzed Stille- (Stille, J.K. *Angew. Chem.* 1986, 68, 504) and Suzuki- couplings (Oh-e, T.; Mijaura, N.; Suzuki, A. *J. Org. Chem.* 1993, 58, 2201). Any other functionalization known for aryl bromides can be employed for introduction of substituents R^{37} and R^{38} .
- v: Removal of the Cbz-group of 173, e.g. by hydrogenation using H_2 and a catalyst such as palladium on charcoal in a suitable solvent such as ethanol, DMF or ethyl acetate.
- 20 vi: Hydrolysis of the ester group, conveniently under acidic conditions, e.g. with 25% aqueous hydrochloric acid in a suitable solvent such as dioxane at an elevated temperature, conveniently at about 100° C.
- vii: The intermediate free amino acid formed is conveniently protected with reagents such as 9-fluorenylmethoxycarbonyl chloride or 9-fluorenylmethoxycarbonyl succinimide using a base such as sodium carbonate or triethylamine in a suitable solvent or mixture of solvents such as dioxane and water, or dichloromethane to yield 174.
- 25

Scheme 36

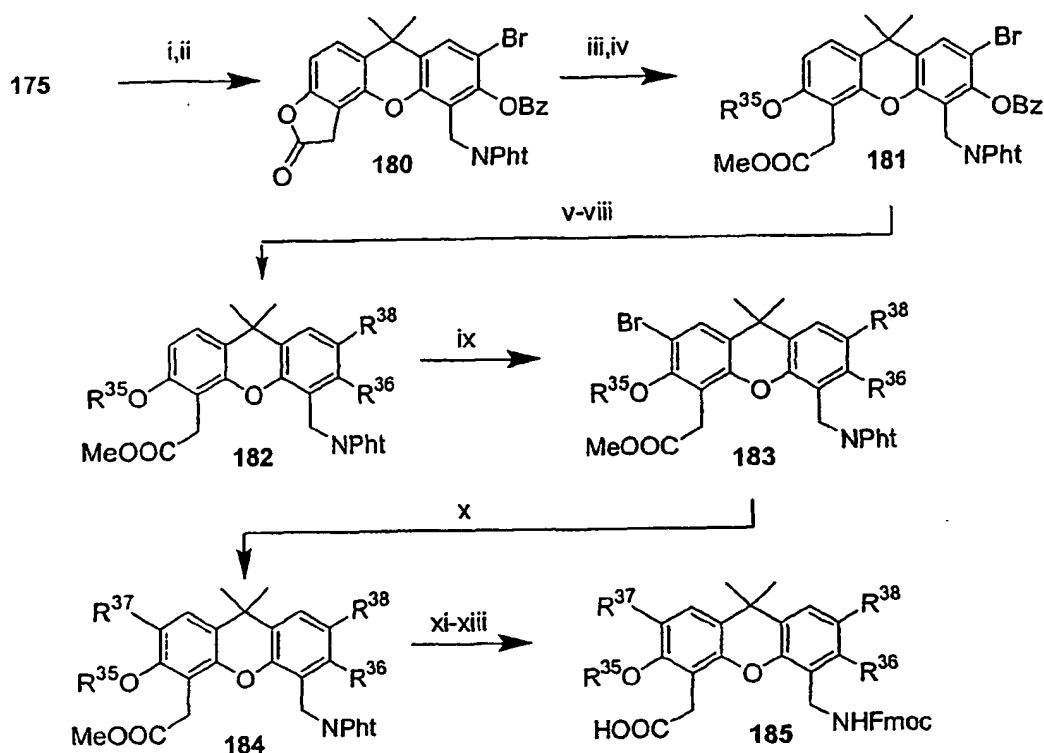


- 5 i: Cleavage of the methoxy groups of 166, preferably by treatment with an excess of boron tribromide in a suitable solvent such as dichloromethane.
- ii: Hydrolysis of the cyano group under acidic conditions, preferably with 25% aqueous hydrochloric acid in a suitable solvent such as dioxane at an elevated temperature, conveniently at about 100° C.
- 10 iii: The resulting acid is treated with a dehydrating agent such as thionyl chloride in a suitable solvent such as dioxane to yield 175.
- iv: Treatment of 175 with an appropriate triflating reagent, preferably trifluoromethanesulfonic acid anhydride in the presence of a base such as 2,6-di-tert-butyl-pyridine in a suitable solvent such as dichloromethane.
- 15 v: Heating of the intermediate, conveniently in a suitable solvent such as methanol.
- vi: Introduction of lower alkyl or aryl-lower alkyl (R^{35}) by alkylation to yield 177. Any other functionalization known for phenol groups can be employed for introduction of substituents R^{35} .
- vii: Introduction of lower alkyl or aryl (R^{36}), conveniently by palladium(0)-catalyzed Suzuki-coupling (Oh-e, T.; Mijaura, N.; Suzuki, A. *J. Org. Chem.* 1993, 58, 2201) to
- 20

yield 178. Any other functionalization known for aryl bromides can be employed for introduction of substituents R³⁶.

- 5 viii: Hydrolysis of the ester group under acidic conditions, conveniently with 25% aqueous hydrochloric acid in a suitable solvent such as dioxane at an elevated temperature, e.g. at about 100° C.
- ix: Cleavage of the phthalimido group, conveniently by hydrazinolysis, e.g. with hydrazine hydrate in a suitable solvent such as ethanol.
- 10 x: The intermediate free amino acid formed is conveniently protected with reagents such as 9-fluorenylmethoxycarbonyl chloride or 9-fluorenylmethoxycarbonyl succinimide using a base such as sodium carbonate or triethylamine in a suitable solvent or mixture of solvents such as dioxane and water, or dichloromethane to yield 179.

Scheme 37

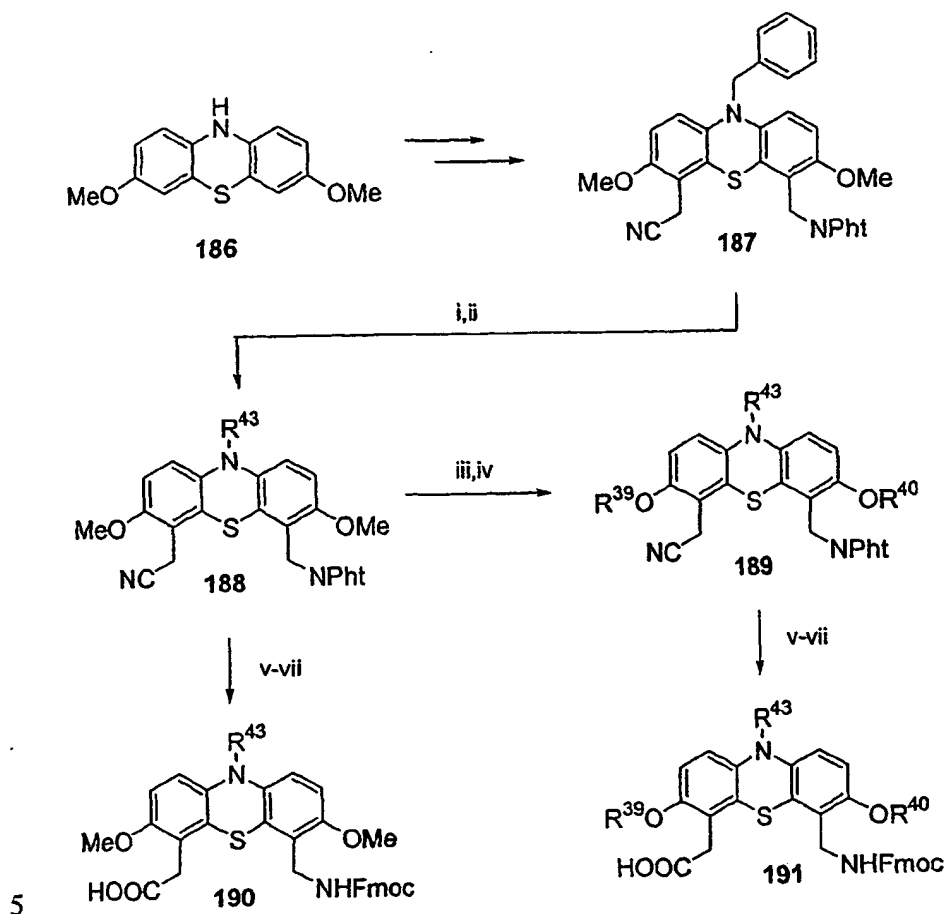


- 5 i: Bromination of 175 using reagents such as bromine in a mixture of acetic acid and dichloromethane at temperatures ranging from about 0° C to about room temperature.
- ii: Benzoylation of the hydroxy group using an appropriate acylating agent such as benzoyl chloride or benzoic acid anhydride, a base such as pyridine or triethylamine and a suitable solvent such as dichloromethane to yield 180.
- 10 iii: 180 is treated with methanol and a catalytic amount of an acidic catalyst such as camphor sulfonic acid under heating.
- iv: Introduction of lower alkyl or aryl-lower alkyl (R^{35}) by alkylation using a base such as sodium hydride or potassium tert.-butoxide in a solvent such as tetrahydrofuran, dimethoxyethane or DMF gives 181.
- 15 v: Lower alkyl, substituted lower alkyl and aryl substituents (R^{38}) are introduced, e.g. by palladium(0)-catalyzed Stille- (Stille, J.K. *Angew. Chem.* 1986, 68, 504) and Suzuki-couplings (Oh-e, T.; Mijaura, N.; Suzuki, A. *J. Org. Chem.* 1993, 58, 2201). Any other functionalization known for aryl bromides can be employed for introduction of substituents R^{38} .
- 20 vi: For cleaving the benzyloxy group the intermediate is conveniently heated with sodium cyanide adsorbed on aluminum oxide and methanol.

- vii: Treatment with an appropriate triflating reagent, preferably trifluoromethanesulfonic acid anhydride, in the presence of a base such as 2,6-di-tert.-butyl-pyridine in a suitable solvent such as dichloromethane.
- 5 viii: Introduction of lower alkyl and aryl substituents (R^{36}), e.g. by palladium(0)-catalyzed Stille- (Stille, J.K. *Angew. Chem.* 1986, 68, 504) and Suzuki- couplings (Oh-e, T.; Mijaura, N.; Suzuki, A. *J. Org. Chem.* 1993, 58, 2201) yields 182. Any other functionalization known for aryl bromides can be employed for introduction of substituents R^{36} .
- 10 ix: Bromination under standard conditions such as using bromine in acetic acid and dichloromethane at temperatures ranging from about 0° C to about room temperature.
- x: Lower alkyl, substituted lower alkyl and aryl substituents (R^{37}) are introduced, e.g. by palladium(0)-catalyzed Stille- (Stille, J.K. *Angew. Chem.* 1986, 68, 504) and Suzuki- couplings (Oh-e, T.; Mijaura, N.; Suzuki, A. *J. Org. Chem.* 1993, 58, 2201) to yield 184. Any other functionalization known for aryl bromides can be employed for
- 15 introduction of substituents R^{37} .
- xi: The ester group is hydrolyzed under acidic conditions, conveniently with 25% aqueous hydrochloric acid in a suitable solvent such as dioxane at an elevated temperature, e.g. at about 100° C.
- xii: The phthalimido group is cleaved, e.g. by hydrazinolysis, conveniently with
- 20 hydrazine hydrate in a suitable solvent such as ethanol.
- xiii: The intermediate free amino acid formed is conveniently protected with reagents such as 9-fluorenylmethoxycarbonyl chloride or 9-fluorenylmethoxycarbonyl succinimide using a base such as sodium carbonate or triethylamine in a suitable solvent or mixture of solvents such as dioxane and water, or dichloromethane to yield 185.

Templates of type (c2) can be prepared as shown in *Schemes 38 and 39*.

Scheme 38

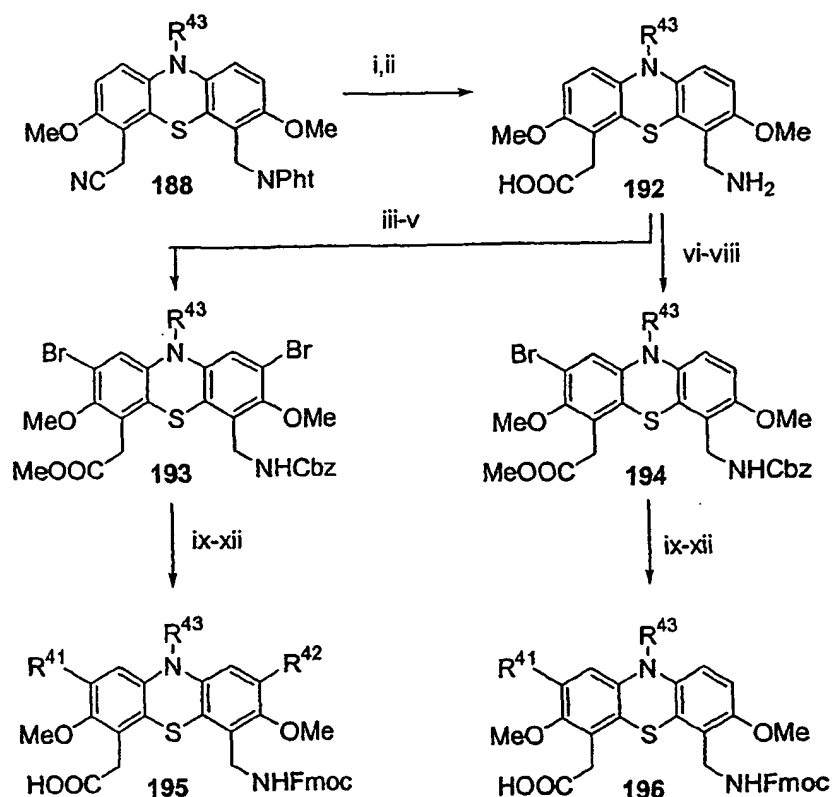


- i: 3,7-Dimethoxyphenothiazine **186** is prepared and converted into **187** according to Müller, K.; Obrecht, D.; Knierzinger, A.; Spiegler, C.; Bannwarth, W.; Trzeciak, A.; Englert, G.; Labhardt, A.; Schönholzer, P. *Perspectives in Medicinal Chemistry*, Editor Testa, B.; Kyburz, E.; Fuhrer, W.; Giger, R.; Weinheim, New York, Basel, Cambridge: Verlag Helvetica Chimica Acta, 1993, 513-531; Bannwarth, W.; Gerber, F.; Grieder, A.; Knierzinger, A.; Müller, K.; Obrecht, D.; Trzeciak, A. *Can. Pat. Appl.* CA2101599(131 pages). The benzyl group is cleaved off from **187** conveniently by hydrogenation, e.g. with H₂ and a catalyst such as palladium on charcoal in a suitable solvent such as ethanol, DMF or ethyl acetate.
- 10
- 15
- ii: Introduction of lower alkyl (R⁴³) by alkylation using an appropriate alkylating agent (R⁴³-X'; X' = OTf, Br, I) and strong bases such as sodium amide in liquid ammonia or sodium hydride in tetrahydrofuran, dioxan or DMF in the presence of a phase transfer catalyst such as TDA-I. In a similar manner substituted lower alkyl (R⁴³) can be

introduced; thus, for example $R^{43} = CH_2COOR^{55}$ and $CH_2CH_2COOR^{55}$ can be introduced by treatment with the appropriate 2-halo acetic and, respectively, 3-halo propionic acid derivatives. Any other functionalization known for diarylamines can be employed for introduction of substituents R^{43} .

- 5 iii: Cleavage of the methoxy groups of 188, conveniently by treatment with an excess of boron tribromide in a suitable solvent such as dichloromethane at temperatures ranging from about -20°C to about room temperature.
- 10 iv: For the introduction of lower alkyl, substituted lower alkyl or aryl-lower alkyl substituents (R^{39} and R^{40}) the intermediate bis-phenol derivative is conveniently reacted with a reagent of the formula R^{39} - and R^{40} - X' ($X' = \text{OTf}, \text{Br}, \text{I}$) in the presence of strong bases such as sodium hydride in tetrahydrofuran, dioxane or DMF in the presence of a phase transfer catalyst such as TDA-L. Any other functionalization known for phenol groups can be employed for introduction of substituents R^{39} and R^{40} .
- 15 v: The cyano group of 188 and, respectively, 189 is hydrolyzed, conveniently under acidic conditions, e.g. with 25% aqueous hydrochloric acid in a suitable solvent such as dioxane at an elevated temperature, e.g. at about 100°C .
- 20 vi: The phthalimide group of the intermediate is cleaved, conveniently by hydrazinolysis, e.g. with hydrazine hydrate in a suitable solvent such as ethanol.
- 20 vii: The free amino group is conveniently protected with reagents such as 9-fluorenylmethoxycarbonyl chloride or 9-fluorenylmethoxycarbonyl succinimide using a base such as sodium carbonate or triethylamine in a suitable solvent or mixture of solvents such as dioxane and water, or dichloromethane to yield 190 and, respectively, 191.

Scheme 39

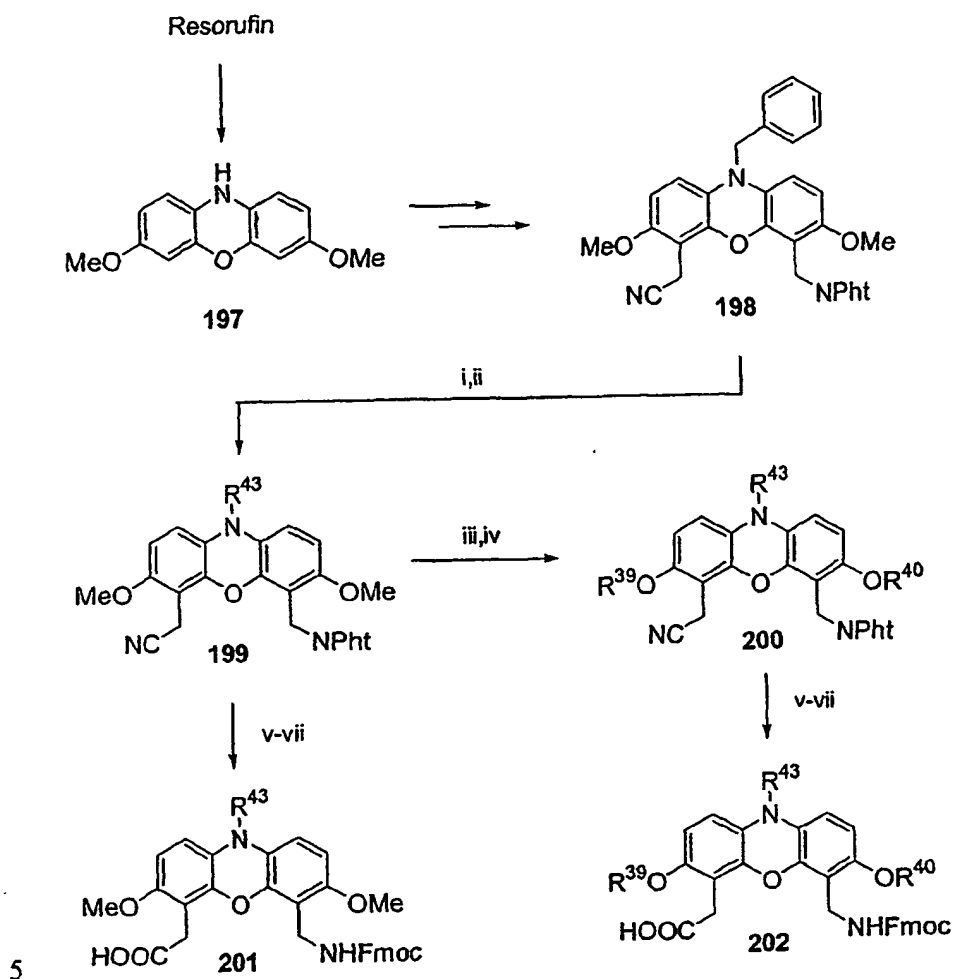


- 5 i: The cyano group of 188 is hydrolyzed, conveniently under acidic conditions, e.g. with 25% aqueous hydrochloric acid in a suitable solvent such as dioxane at an elevated temperature, e.g. at about 100° C.
- ii: The phthalimide group of the intermediate is cleaved, conveniently by hydrazinolysis, e.g. with hydrazine hydrate in a suitable solvent such as ethanol to yield 192.
- 10 iii: Double ortho- bromination of 192 is performed preferably with excess bromine in acetic acid and dichloromethane. In a similar fashion $R^{41} = R^{42} = NO_2$ can be introduced by treatment with HNO_3 in acetic acid and $R^{41} = R^{42} = CH_2-NPht$ by treatment with hydroxymethyl phthalimide in H_2SO_4 . Any other functionalization by electrophilic aromatic substitution known can be employed for introduction of
- 15 substituents R^{41} and R^{42} .
- iv: The amino group is protected, conveniently Cbz-protected, with reagents such as benzyloxycarbonyl chloride or succinimide in a suitable solvent such as dioxane in the presence of a base such as aqueous sodium hydroxide.
- v: The carboxylic acid group is esterified, preferably with DBU and methyl iodide in
- 20 DMF to yield 193.

- vi: Regioselective bromination of 192 is performed preferably with bromine in acetic acid and dichloromethane. In a similar fashion $R^{41} = NO_2$ can be introduced by treatment with HNO_3 in acetic acid and $R^{41} = CH_2-NPt$ by treatment with hydroxymethyl phthalimide in H_2SO_4 . Any other functionalization by electrophilic aromatic substitution known can be employed for introduction of substituents R^{41} .
- 5 vii: The amino group is conveniently Cbz-protected with reagents such as benzyloxycarbonyl chloride or succinimide in a suitable solvent such as dioxane in presence of a base such as aqueous sodium hydroxide.
- 10 viii: The carboxylic acid group is esterified, preferably with DBU and methyl iodide in DMF to yield 194.
- ix: Introduction of lower alkyl, substituted lower alkyl and aryl substituents (R^{41}) for 194 and (R^{41} and R^{42}) for 193, conveniently by palladium(0)-catalyzed Stille- (Stille, J.K. *Angew. Chem.* 1986, 68, 504) and Suzuki- couplings (Oh-e, T.; Mijaura, N.; Suzuki, A. *J. Org. Chem.* 1993, 58, 2201). Any other functionalization known for aryl bromides can be employed for introduction of substituents R^{41} and R^{42} .
- 15 x: Removal of the Cbz-group, e.g. by hydrogenation using H_2 and a catalyst such as palladium on charcoal in a suitable solvent such as ethanol, DMF and ethyl acetate.
- xi: Hydrolysis of the ester group, conveniently under acidic conditions, e.g. with 25% aqueous hydrochloric acid in a suitable solvent such as dioxane at an elevated temperature, preferably at about 100° C.
- 20 xii: The intermediate free amino acid formed is conveniently protected with reagents such as 9-fluorenylmethoxycarbonyl chloride or 9-fluorenylmethoxycarbonyl succinimide using a base such as sodium carbonate or triethylamine in a suitable solvent or mixture of solvents such as dioxane and water, or dichloromethane to yield 195 and
- 25 196.

Templates of type (c3) can be prepared as shown in *Schemes 40 and 41*.

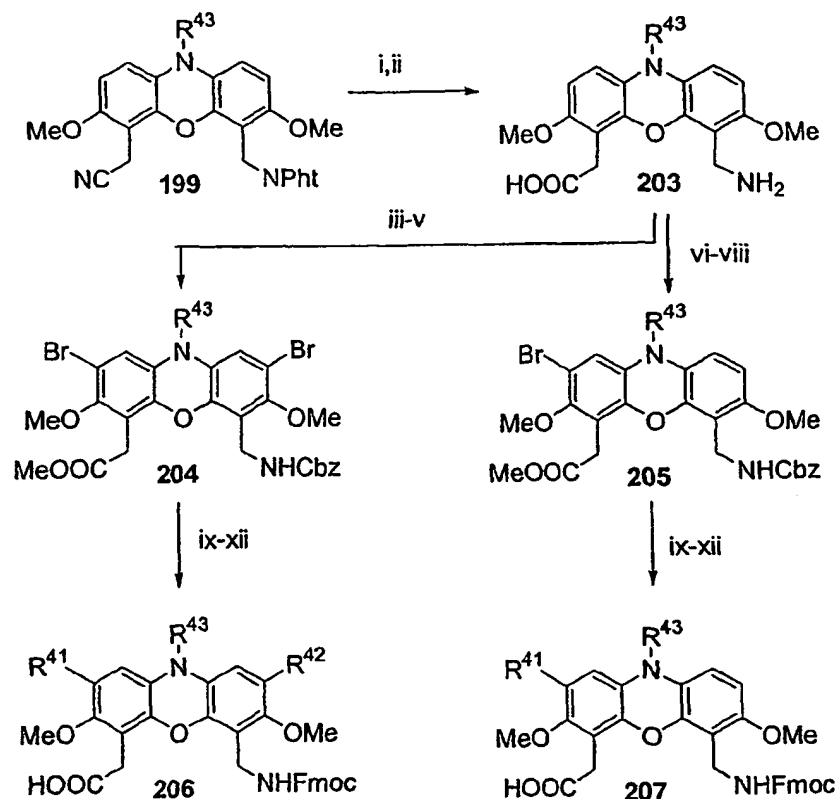
Scheme 40



- i: 197 can be prepared from commercial resorufin and converted into 198 according to Müller, K.; Obrecht, D.; Knierzinger, A.; Spiegler, C.; Bannwarth, W.; Trzeciak, A.; Englert, G.; Labhardt, A.; Schönholzer, P. *Perspectives in Medicinal Chemistry*, Editor Testa, B.; Kyburz, E.; Fuhrer, W.; Giger, R., Weinheim, New York, Basel, Cambridge: Verlag Helvetica Chimica Acta, 1993, 513-531; Bannwarth, W.; Gerber, F.; Grieder, A.; Knierzinger, A.; Müller, K.; Obrecht, D.; Trzeciak, A. *Can. Pat. Appl.* CA2101599(131 pages). For splitting off the benzyl group 198 is conveniently hydrogenated e.g. with H₂ and a catalyst such as palladium on charcoal in a suitable solvent such as ethanol, DMF or ethyl acetate.
- 10
- 15

- ii: Introduction of lower alkyl (R^{43}) by alkylation with $R^{43}-X'$ ($X' = OTf, Br, I$) using strong bases such as sodium amide in liquid ammonia or sodium hydride in tetrahydrofuran, dioxan or DMF in the presence of a phase transfer catalyst such as TDA-I to yield 199. In a similar manner substituted lower alkyl (R^{43}) can be introduced; thus, for example, $R^{43} = CH_2COOR^{55}$ and $CH_2CH_2COOR^{55}$ can be introduced by treatment with the appropriate 2-halo acetic and, respectively, 3-halo propionic acid derivatives. Any other functionalization of diarylamino groups known can be employed for introduction of substituents R^{43} .
- 10 iii: Cleavage of the methoxy groups of 199, conveniently by treatment with excess boron tribromide in dichloromethane at temperatures ranging from about -20° to about room temperature.
- 15 iv: The intermediate bis-phenol derivative is preferably reacted with R^{39} and $R^{40}-X'$ ($X' = OTf, Br, I$) in the presence of strong bases such as sodium hydride in tetrahydrofuran, dioxan or DMF in the presence of a phase transfer catalyst such as TDA-I. Any other functionalization for phenol groups can be employed for introduction of substituents R^{39} and R^{40} .
- v: The cyano group of 199 and, respectively, 200 is hydrolyzed under acidic conditions, e.g. with 25% aqueous hydrochloric acid in a suitable solvent such as dioxane at an elevated temperature, conveniently at about $100^\circ C$.
- 20 vi: The phthalimide group is cleaved, conveniently by hydrazinolysis, e.g. with hydrazine hydrate in suitable solvent such as ethanol.
- vii: The free amino group is conveniently protected with reagents such as 9-fluorenylmethoxycarbonyl chloride or 9-fluorenylmethoxycarbonyl succinimide using a base such as sodium carbonate or triethylamine in suitable solvent or mixture of solvents such as dioxane and water, or dichloromethane to yield 201 and, respectively, 202.
- 25

Scheme 41



- 5 i: The cyano group of 199 is hydrolyzed, conveniently under acidic conditions, e.g. with 25% aqueous hydrochloric acid in a suitable solvent such as dioxane at an elevated temperature, e.g. at about 100° C.
- ii: The phthalimide group of the intermediate is cleaved, conveniently by hydrazinolysis, e.g. with hydrazine hydrate in a suitable solvent such as ethanol to yield 203.
- 10 iii: Double ortho- bromination of 203 is performed preferably with excess bromine in acetic acid and dichloromethane. In a similar fashion $R^{41} = R^{42} = NO_2$ can be introduced by treatment with HNO_3 in acetic acid and $R^{41} = R^{42} = CH_2-NPhT$ by treatment with hydroxymethyl phthalimide in H_2SO_4 . Any other functionalization by electrophilic aromatic substitution can be employed for introduction of substituents R^{41} and R^{42} .
- 15 iv: The amino group is protected, conveniently Cbz-protected, with reagents such as benzyloxycarbonyl chloride or succinimide in a suitable solvent such as dioxane in the presence of a base such as aqueous sodium hydroxide.
- v: The carboxylic acid group is esterified, preferably with DBU and methyl iodide in
- 20 DMF to yield 204.

- vi: Regioselective bromination of 203 is performed preferably with bromine in acetic acid and dichloromethane. In a similar fashion $R^{41} = NO_2$ can be introduced by treatment with HNO_3 in acetic acid and $R^{41} = CH_2-NPht$ by treatment with hydroxymethyl phthalimide in H_2SO_4 .
- 5 vii: The amino group is conveniently Cbz-protected with reagents such as benzyloxycarbonyl chloride or succinimide in a suitable solvent such as dioxane in presence of a base such as aqueous sodium hydroxide.
- viii: The carboxylic acid group is esterified, preferably with DBU and methyl iodide in DMF to yield 205.
- 10 ix: Introduction of lower alkyl, substituted lower alkyl and aryl substituents (R^{41}) for 205 and (R^{41} and R^{42}) for 204, conveniently by palladium(0)-catalyzed Stille- (Stille, J.K. *Angew. Chem.* 1986, 68, 504) and Suzuki- couplings (Oh-e, T.; Mijaura, N.; Suzuki, A. *J. Org. Chem.* 1993, 58, 2201). Any other functionalization known for aryl bromides can be employed for introduction of substituents R^{41} and R^{42} .
- 15 x: Removal of the Cbz-group, e.g. by hydrogenation using H_2 and a catalyst such as palladium on charcoal in a suitable solvent such as ethanol, DMF and ethyl acetate.
- xi: Hydrolysis of the ester group, conveniently under acidic conditions, e.g. with 25% aqueous hydrochloric acid in a suitable solvent such as dioxane at an elevated temperature, preferably at about 100° C.
- 20 xii: The intermediate free amino acid formed is conveniently protected with reagents such as 9-fluorenylmethoxycarbonyl chloride or 9-fluorenylmethoxycarbonyl succinimide using a base such as sodium carbonate or triethylamine in a suitable solvent or mixture of solvents such as dioxane and water, or dichloromethane to yield 206 and 207.

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Templates(d) can be prepared according to D. Obrecht, U. Bohdal, C. Lehmann, P. Schönholzer, K. Müller, *Tetrahedron* 1995, 51, 10883; D. Obrecht, C. Abrecht, M. Altorfer, U. Bohdal, A. Grieder, M. Kleber, P. Pfyffer, K. Müller, *Helv. Chim. Acta* 1996, 79, 1315-1337.

30

Templates (e1) and (e2): See R. Mueller, L. Revesz, *Tetrahedron Lett.* 1994, 35, 4091; H.-G. Lubell, W. D. Lubell, *J. Org. Chem.* 1996, 61, 9437; L. Colombo, M. DiGiacomo, G. Papeo, O. Carugo, C. Scolastico, L. Manzoni, *Tetrahedron Lett.* 1994, 35, 4031.

35

Templates (e3): See S. Hanessian, B. Ronan, A. Laoui, *Bioorg. Med. Chem. Lett.* 1994, 4, 1397.

- Templates (e4): See S. Hanessian, G. McNaughton-Smith, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1567.
- 5
Templates (f): See T.P. Curran, P. M. McEnay, *Tetrahedron Lett.* **1995**, *36*, 191-194.
- Templates (g): See D. Gramberg, C. Weber, R. Beeli, J. Inglis, C. Bruns, J. A. Robinson, *Helv. Chem. Acta* **1995**, *78*, 1588-1606; K. H. Kim, J. P. Dumas, J. P. Germanas, *J. Org. Chem.* **1996**, *61*, 3138-3144.
- 10
Templates (h): See S. de Lombart, L. Blanchard, L. B. Stamford, D. M. Sperbeck, M. D. Grim, T. M. Jenson, H. R. Rodriguez, *Tetrahedron Lett.* **1994**, *35*, 7513-7516.
- Templates (i1): See J. A. Robl, D. S. Karanewski, M. M. Asaad, *Tetrahedron Lett.* **1995**, *5*, 773-758.
- 15
Templates (i2): See T. P. Burkholder, T.-B. Le, E. L. Giroux, G. A. Flynn, *Bioorg. Med. Chem. Lett.* **1992**, *2*, 579.
- Templates (i3) and (i4): See L. M. Simpkins, J. A. Robl, M. P. Cimarusti, D. E. Ryono, J. Stevenson, C.-Q. Sun, E. W. Petrillo, D. S. Karanewski, M. M. Asaad, J. E. Bird, T. R. Schaeffer, N. C. Trippodo, Abstracts of papers, 210th Am. Chem. Soc Meeting, Chicago, 111, MEDI 064 (1995).
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Templates (k): See D. Benlshai, A. R. McMurray, *Tetrahedron* **1993**, *49*, 6399.
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Templates (l): See E. G. von Roeder, H. Kessler, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 687-689.
- Templates (m): See R. Gonzalez-Muniz, M. J. Dominguez, M. T. Garcia-Lopez, *Tetrahedron* **1992**, *48*, 5191-5198.
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Templates (n): See F. Esser, A. Carpy, H. Briem, H. Köppen, K.-H. Pook, *Int. J. Pept. Res.* **1995**, *45*, 540-546.
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Templates (o): See N. De la Figuera, I. Alkorta, T. Garcia-Lopez, R. Herranz, R. Gonzalez-Muniz, *Tetrahedron* **1995**, *51*, 7841.

Templates (p): See U. Slomczynska, D. K. Chalmers, F. Cornille, M. L. Smythe, D. D. Benson, K. D. Moeller, G. R. Marshall, *J. Org. Chem.* **1996**, *61*, 1198-1204.

5 The β -hairpin peptidomimetics of the invention can be used in a wide range of applications in order to inhibit the growth of or to kill microorganisms and/or cancer cells.

They can be used for example as disinfectants or as preservatives for materials such as foodstuffs, cosmetics, medicaments and other nutrient-containing materials or for preventing surfaces from microbial colonization [J. M. Schierholz, C. Fleck, J. Beuth, G. Pulverer, J. *Antimicrob. Chemother.*, **2000**, *46*, 45-50]. The β -hairpin peptidomimetics of the invention
10 can also be used to treat or prevent diseases related to microbial infection in plants and animals.

For use as disinfectants or preservatives the β -hairpin peptidomimetics can be added to the
15 desired material singly, as mixtures of several β -hairpin peptidomimetics or in combination with other antimicrobial agents. The β -hairpin peptidomimetics may be administered per se or may be applied as an appropriate formulation together with carriers, diluents or excipients well known in the art, expediently in a form suitable for oral, topical, transdermal, injection, buccal, transmucosal, pulmonary or inhalation administration, such as tablets, dragees,
20 capsules, solutions, liquids, gels, plasters, creams, ointments, syrups, slurries, suspensions, sprays, nebulisers or suppositories.

When used to treat or prevent infections or diseases related to such infections or cancer, the β -hairpin peptidomimetics can be administered singly, as mixtures of several β -hairpin
25 peptidomimetics, in combination with other antimicrobial, antibiotic or anticancer agents or in combination with other pharmaceutically active agents. The β -hairpin peptidomimetics can be administered per se or as pharmaceutical compositions.

Pharmaceutical compositions comprising β -hairpin peptidomimetics of the invention may be
30 manufactured by means of conventional mixing, dissolving, granulating, coated tablet-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes. Pharmaceutical compositions may be formulated in conventional manner using one or more physiologically acceptable carriers, diluents, excipients or auxiliaries which facilitate processing of the active β -hairpin peptidomimetics into preparations which can be used
35 pharmaceutically. Proper formulation depends upon the method of administration chosen.

For topical administration the β -hairpin peptidomimetics of the invention may be formulated as solutions, gels, ointments, creams, suspensions, etc. as are well-known in the art.

Systemic formulations include those designed for administration by injection, e.g.

- 5 subcutaneous, intravenous, intramuscular, intrathecal or intraperitoneal injection, as well as those designed for transdermal, transmucosal, oral or pulmonary administration.

- 10 For injections, the β -hairpin peptidomimetics of the invention may be formulated in adequate solutions, preferably in physiologically compatible buffers such as Hink's solution, Ringer's solution, or physiological saline buffer. The solution may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the β -hairpin peptidomimetics of the invention may be in powder form for combination with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

- 15 For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation as known in the art.

- For oral administration, the compounds can be readily formulated by combining the active β -hairpin peptidomimetics of the invention with pharmaceutically acceptable carriers well known in the art. Such carriers enable the β -hairpin peptidomimetics of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions etc., for oral ingestion of a patient to be treated. For oral formulations such as, for example, powders, capsules and tablets, suitable excipients include fillers such as sugars, such as lactose, sucrose, mannitol and sorbitol; cellulose preparations such as maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP); granulating agents; and binding agents. If desired, disintegrating agents may be added, such as cross-linked polyvinylpyrrolidones, agar, or alginic acid or a salt thereof, such as sodium alginate. If desired, solid dosage forms may be sugar-coated or enteric-coated using standard techniques.
- 20
25
30

For oral liquid preparations such as, for example, suspensions, elixirs and solutions, suitable carriers, excipients or diluents include water, glycols, oils, alcohols, etc. In addition, flavoring agents, preservatives, coloring agents and the like may be added.

For buccal administration, the composition may take the form of tablets, lozenges, etc. formulated as usual.

For administration by inhalation, the β -hairpin peptidomimetics of the invention are
5 conveniently delivered in form of an aerosol spray from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, carbon dioxide or another suitable gas. In the case of a pressurized aerosol the dose unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of
10 the β -hairpin peptidomimetics of the invention and a suitable powder base such as lactose or starch.

The compounds may also be formulated in rectal or vaginal compositions such as suppositories together with appropriate suppository bases such as cocoa butter or other
15 glycerides.

In addition to the formulation described previously, the β -hairpin peptidomimetics of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (e.g. subcutaneously or intramuscularly) or by intramuscular
20 injection. For the manufacture of such depot preparations the β -hairpin peptidomimetics of the invention may be formulated with suitable polymeric or hydrophobic materials (e.g. as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble salts.

In addition, other pharmaceutical delivery systems may be employed such as liposomes and emulsions well known in the art. Certain organic solvents such as dimethylsulfoxide also may be employed. Additionally, the β -hairpin peptidomimetics of the invention may be delivered using a sustained-release system, such as semipermeable matrices of solid polymers containing the therapeutic agent. Various sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on
30 their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic agent, additional strategies for protein stabilization may be employed.

As the β -hairpin peptidomimetics of the invention may contain charged residues, they may be
35 included in any of the above-described formulations as free bases or as pharmaceutically

acceptable salts. Pharmaceutically acceptable salts tend to be more soluble in aqueous and other protic solvents than are the corresponding free base forms.

5 The β -hairpin peptidomimetics of the invention, or compositions thereof, will generally be used in an amount effective to achieve the intended purpose. It is to be understood that the amount used will depend on a particular application.

10 For example, for use as a disinfectant or preservative, an antimicrobially effective amount of a β -hairpin peptidomimetic of the invention, or a composition thereof, is applied or added to the material to be disinfected or preserved. By antimicrobially effective amount is meant an amount of a β -hairpin peptidomimetic of the invention or composition that inhibits the growth of, or is lethal to, a target microbe population. While the antimicrobially effective amount will depend on a particular application, for use as disinfectants or preservatives the β -hairpin peptidomimetics of the invention, or compositions thereof, are usually added or applied to the
15 material to be disinfected or preserved in relatively low amounts. Typically, the β -hairpin peptidomimetics of the invention comprise less than about 5% by weight of a disinfectant solution or material to be preserved, preferably less than 1% by weight and more preferably less than 0.1% by weight. An ordinary skilled expert will be able to determine antimicrobially effective amounts of particular β -hairpin peptidomimetics of the invention for particular
20 applications without undue experimentation using, for example, the in vitro assays provided in the examples.

For use to treat or prevent microbial infections or diseases related thereto and cancer, the β -hairpin peptidomimetics of the invention, or compositions thereof, are administered or applied
25 in a therapeutically effective amount. By therapeutically effective amount is meant an amount effective in ameliorating the symptoms of, or ameliorate, treat or prevent microbial infections or diseases related thereto. Determination of a therapeutically effective amount is well within the capacities of those skilled in the art, especially in view of the detailed disclosure provided herein.

30 As in the case of disinfectants and preservatives, for topical administration to treat or prevent bacterial, yeast, fungal or other infections a therapeutically effective dose can be determined using, for example, the in vitro assays provided in the examples. The treatment may be applied while the infection is visible, or even when it is not visible. An ordinary skilled expert
35 will be able to determine therapeutically effective amounts to treat topical infections without undue experimentation.

For systemic administration, a therapeutically effective dose can be estimated initially from in vitro assays. For example, a dose can be formulated in animal models to achieve a circulating β -hairpin peptidomimetic concentration range that includes the IC_{50} as determined in the cell culture (i.e. the concentration of a test compound that is lethal to 50% of a cell culture), the MIC, as determined in cell culture (i.e. the concentration of a test compound that is lethal to 100% of a cell culture). Such information can be used to more accurately determine useful doses in humans.

Initial dosages can also be determined from in vivo data, e.g. animal models, using techniques that are well known in the art. One having ordinary skills in the art could readily optimize administration to humans based on animal data.

Dosage amount for applications as antimicrobial agents may be adjusted individually to provide plasma levels of the β -hairpin peptidomimetics of the invention which are sufficient to maintain the therapeutic effect. Usual patient dosages for administration by injection range from about 0.1-5mg/kg/day, preferably from about 0.5 to 1 mg/kg/day. Therapeutically effective serum levels may be achieved by administering multiple doses each day.

In cases of local administration or selective uptake, the effective local concentration of the β -hairpin peptidomimetics of the invention may not be related to plasma concentration. One having the skills in the art will be able to optimize therapeutically effective local dosages without undue experimentation.

The amount of β -hairpin peptidomimetics administered will, of course, be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration and the judgement of the prescribing physician.

The antimicrobial therapy may be repeated intermittently while infections are detectable or even when they are not detectable. The therapy may be provided alone or in combination with other drugs, such as for example antibiotics or other antimicrobial agents.

Normally, a therapeutically effective dose of the β -hairpin peptidomimetics described herein will provide therapeutic benefit without causing substantial toxicity.

Hemolysis of red blood cells is often employed for assessment of toxicity of related compounds such as *protegrin* or *tachyplesin*. Values are given as %-lysis of red blood cells observed at a concentration of 100µg/ml. Typical values determined for cationic peptides such as *protegrin* and *tachyplesin* range between 30-40% with average MIC-values of 1-5 µg/ml over a wide range of pathogens. Normally, β-hairpin peptidomimetics of the invention will show hemolysis in a range of 0.5-10%, often in a range of 1-5%, at activity levels comparable to those mentioned above for *protegrin* and *tachyplesin*. Thus preferred compounds exhibit low MIC-values and low %-hemolysis of red blood cells observed at a concentration of 100µg/ml.

10

Toxicity of the β-hairpin peptidomimetics of the invention herein can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., by determining the LD₅₀ (the dose lethal to 50% of the population) or the LD₁₀₀ (the dose lethal to 100% of the population). The dose ratio between toxic and therapeutic effect is the therapeutic index. Compounds which exhibit high therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in formulating a dosage range that is not toxic for use in humans. The dosage of the β-hairpin peptidomimetics of the invention lies preferably within a range of circulating concentrations that include the effective dose with little or no toxicity. The dosage may vary within the range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dose can be chosen by the individual physician in view of the patient's condition (see, e.g. Fingl et al. 1975, In : *The Pharmacological Basis of Therapeutics*, Ch.1, p.1).

20

The following Examples illustrate the invention in more detail but are not intended to limit its scope in any way. The following abbreviations are used in these Examples:

HBTU : 1-benzotriazol-1-yl-tetramethyluronium hexafluorophosphate

5 (Knorr et al. *Tetrahedron Lett.* 1989, 30, 1927-1930)

HOBt : 1-hydroxybenzotriazole

DIEA : diisopropylethylamine

HOAT: 7-aza-1-hydroxybenzotriazole

HATU: O-(7-aza-benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate

10 Carpino et al. *Tetrahedron Lett.* 1994, 35, 2279-2281)

Examples

1. Peptide synthesis

15

Coupling of the first protected amino acid residue

0.5 g of 2-chlorotriylchloride resin (Barlos et al. *Tetrahedron Lett.* 1989, 30, 3943-3946) (0.83 mMol/g, 0.415 mmol) was filled into a dried flask. The resin was suspended in CH₂Cl₂ (2.5 ml) and allowed to swell at room temperature under constant stirring. The resin was
20 treated with 0.415 mMol (1eq) of the first suitably protected amino acid residue (see below) and 284 µl (4eq) of diisopropylethylamine (DIEA) in CH₂Cl₂ (2.5 ml), the mixture was shaken at 25°C for 15 minutes, poured onto the pre-swollen resin and stirred at 25°C for 18 hours. The resin colour changed to purple and the solution remained yellowish. The resin was
25 washed extensively (CH₂Cl₂ /MeOH/DIEA : 17/2/1; CH₂Cl₂, DMF; CH₂Cl₂; Et₂O, 3 times each) and dried under vacuum for 6 hours.

Loading was typically 0.6-0.7 mMol/g.

The following preloaded resins were prepared: Fmoc-GlyO-chlorotriylresin; Fmoc-Arg(Pbf)O-chlorotriylresin; Fmoc-Lys(Boc)O-chlorotriylresin.

30

1.1. Procedure 1

The synthesis was carried out using a Syro-peptide synthesizer (MultisynTech) using 24 to 96 reaction vessels. In each vessel was placed 60 mg (weight of the resin before loading) of the above resin. The following reaction cycles were programmed and carried out:

	Step	Reagent	Time
	1	CH ₂ Cl ₂ , wash and swell (manual)	3 x 1 min.
10	2	DMF, wash and swell	1 x 5 min
	3	40 % piperidine/DMF	1 x 5 min.
	4	DMF, wash	5 x 2 min.
	5	5 equiv. Fmoc amino acid/DMF + 5 eq. HBTU	
15		+ 5 eq. HOBt + 5 eq. DIEA	1 x 120 min.
	6	DMF, wash	4 x 2 min.
	7	CH ₂ Cl ₂ , wash (at the end of the synthesis)	3 x 2 min.

Steps 3 to 6 are repeated to add each amino-acid.

Cleavage of the fully protected peptide fragment

After completion of the synthesis, the resin was suspended in 1 ml (0.39 mMol) of 1% TFA in CH₂Cl₂ (v/v) for 3 minutes, filtered and the filtrate was neutralized with 1ml (1.17 mMol, 3eq.) of 20% DIEA in CH₂Cl₂ (v/v). This procedure was repeated twice to ensure completion of the cleavage. The filtrate was evaporated to dryness and the product was fully deprotected to be analyzed by reverse phase-HPLC (column C₁₈) to monitor the efficiency of the linear peptide synthesis.

Cyclization of the linear peptide

100 mg of the fully protected linear peptide were dissolved in DMF (9 ml, conc. 10 mg/ml). Then 41.8 mg (0.110 mMol, 3 eq.) of HATU, 14.9 mg (0.110 mMol, 3 eq) of HOAt and 1 ml (0.584 mMol) of 10% DIEA in DMF (v/v) were added and the mixture vortexed at 20°C for 16 hours and subsequently concentrated under high vacuum. The residue was partitioned

between CH_2Cl_2 and $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ (90/10: v/v). The CH_2Cl_2 phase was evaporated to yield the fully protected cyclic peptide.

Deprotection and purification of the cyclic peptide:

5

The cyclic peptide obtained was dissolved in 1 ml of the cleavage mixture containing 95% trifluoroacetic acid (TFA), 2.5% water and 2.5% triisopropylsilane (TIS). The mixture was left to stand at 20°C for 2.5 hours and then concentrated under vacuum. The residue was dissolved in a solution of H_2O /acetic acid (75/25: v/v) and the mixture extracted with di-

10 isopropylether.

The water phase was dried under vacuum and then the product purified by preparative reverse phase HPLC.

After lyophilisation products were obtained as a white powder and analysed by ESI-MS. The analytical data comprising HPLC retention times and ESI-MS are shown in tables 1-7.

15

Analytical HPLC retention times (RT, in minutes) were determined using a VYDAC 218TP104 (length 25cm) column with *gradient A*: (10% CH_3CN + 0.1% TFA and 90% H_2O + 0.1% TFA to 98% CH_3CN + 0.1% TFA and 2% H_2O + 0.1% TFA in 20minutes) and with *gradient B*: (10% CH_3CN + 0.1% TFA and 90% H_2O + 0.1% TFA to 98% CH_3CN + 0.1% TFA and 2% H_2O + 0.1% TFA in 21minutes).

20

Examples ex.1-7 ($n=8$) are shown in *table 1*. The peptides were synthesized starting with the amino acid at position P4 which was coupled to the resin. Starting resins were Fmoc-Arg(Pbf)O-chlorotritylresin and Fmoc-Lys(Boc)O-chlorotritylresin, which were prepared as described above. The linear peptides were synthesized on solid support according to **procedure 1** in the following sequence: P5-P6-P7-P8- $^{\text{D}}$ Pro-Pro-P1-P2-P3-P4-resin, cleaved, cyclized, deprotected and purified as indicated. HPLC-retention times (minutes) were determined using *gradient A*.

25

Examples ex.8-31 ($n=9$) are shown in *table 2*. The peptides were synthesized starting with the amino acid at position P5 which was coupled to the resin. Starting resin was Fmoc-Arg(Pbf)O-chlorotritylresin, which was prepared as described above. The linear peptides were synthesized on solid support according to **procedure 1** in the following sequence: P6-P7-P8-P9- $^{\text{D}}$ Pro-Pro-P1-P2-P3-P4-P5-resin, cleaved, cyclized, deprotected and purified as indicated. HPLC-retention times (minutes) were determined using *gradient A*.

30

35

Examples ex.32-58 ($n=10$) are shown in *table 3*. The peptides were synthesized starting with the amino acid at position P5 which was coupled to the resin. Starting resin was Fmoc-

Arg(Pbf)O-chlorotritylresin, which was prepared as described above. The linear peptides were synthesized on solid support according to **procedure 1** in the following sequence: P6-P7-P8-P9-P10-^DPro-Pro-P1-P2-P3-P4-P5-resin, cleaved, cyclized, deprotected and purified as indicated. HPLC-retention times (minutes) were determined using *gradient A*.

5

Examples ex.59-70 (n=11) are shown in *table 4*. The peptides were synthesized starting with the amino acid at position P5 which was coupled to the resin. Starting resin was Fmoc-Arg(Pbf)O-chlorotritylresin, which was prepared as described above. The linear peptides were synthesized on solid support according to **procedure 1** in the following sequence: P6-P7-P8-P9-P10-P11-^DPro-Pro-P1-P2-P3-P4-P5-resin, cleaved, cyclized, deprotected and purified as indicated. HPLC-retention times (minutes) were determined using *gradient A*.

10

Examples ex.71-84 (n=14) are shown in *table 5*. The peptides were synthesized starting with the amino acid at position P7 which was coupled to the resin. Starting resin was Fmoc-Arg(Pbf)O-chlorotritylresin, which was prepared as described above. The linear peptides were synthesized on solid support according to **procedure 1** in the following sequence: P8-P9-P10-P11-P12-P13-P14-^DPro-Pro-P1-P2-P3-P4-P5-P6-P7-resin, cleaved, cyclized, deprotected and purified as indicated. HPLC-retention times (minutes) were determined using *gradient A*.

15

Examples ex.85-95 (n=16) are shown in *table 6*. The peptides were synthesized starting with the amino acid at position P8 which was coupled to the resin. Starting resins were Fmoc-Arg(Pbf)O-chlorotritylresin and Fmoc-Lys(Boc)O-chlorotritylresin, which were prepared as described above. The linear peptides were synthesized on solid support according to **procedure 1** in the following sequence: P9-P10-P11-P12-P13-P15-P16-^DPro-Pro-P1-P2-P3-P4-P5-P6-P7-P8-resin, cleaved, cyclized, deprotected and purified as indicated. HPLC-retention times (minutes) were determined using *gradient A*.

20

25

Examples ex.96-246, ex.276 (n=12) are shown in *table 7*. The peptides (except ex.177 and ex.181) were synthesized starting with the amino acid at position P6 which was grafted to the resin. Starting resins were Fmoc-Arg(Pbf)O-chlorotritylresin and Fmoc-Lys(Boc)O-chlorotritylresin, which were prepared as described above. The linear peptides were synthesized on solid support according to **procedure 1** in the following sequence: P7-P8-P9-P10-P11-P12-^DPro-Pro-P1-P2-P3-P4-P5-P6-resin, cleaved, cyclized, deprotected and purified as indicated. HPLC-retention times (minutes) were determined using *gradient A*.

30

35

Examples ex.177 to ex.181 (n=12) are shown in *table 7*. The peptides were synthesized starting with the amino acid at position P7 which was coupled to the resin. Starting resin was

Fmoc-Arg(Pbf)O-chlorotritylresin, which were prepared as described above. The linear peptides were synthesized on solid support according to **procedure 1** in the following sequence: P8-P9-P10-P11-P12-^DPro-Pro-P1-P2-P3-P4-P5-P6-P7-resin, cleaved, cyclized, deprotected and purified as indicated. HPLC-retention times (minutes) were determined using
5 *gradient A*.

Examples ex.247-277 (n=12) are shown in *table 7*. The peptides were synthesized starting with the amino acid at position P6 which was grafted to the resin. Starting resins were Fmoc-Arg(Pbf)O-chlorotritylresin and Fmoc-Lys(Boc)O-chlorotritylresin, which were prepared as
10 described above. The linear peptides were synthesized on solid support according to **procedure 1** in the following sequence: P7-P8-P9-P10-P11-P12-^DPro-BB-P1-P2-P3-P4-P5-P6-resin, cleaved, cyclized, deprotected and purified as indicated.
BB: Gly (ex.247); Arg(Pmc) (ex.248); Y(Bzl) (ex.249); Phe (ex.250); Trp (ex.251); Leu (ex.252); Ile (ex.253); Cha (ex.254); 2-Nal (ex.255); 219a (ex.256); 219b (ex.257); 219c
15 (ex.258); 219d (ex.259); 219e (ex.260); 219f (ex.261); 219g (ex.262); 219h (ex.263); 219i (ex.264); 219k (ex.265); 219l (ex.266); 219m(ex.267); 219n (ex.268); 219o (ex.269); 219p (ex.270); 219q (ex.271); 219r (ex.272); 219s (ex.273); 219t (ex.274); 219u (ex.275).
Building blocks 219a-u are described below.

Example ex.277 (n=12) is shown in *table 7*. The peptide was synthesized starting with the amino acid at position P6 which was grafted to the resin. Starting resin was Fmoc-Arg(Pbf)O-chlorotritylresin, which were prepared as described above. The linear peptide was synthesized on solid support according to **procedure 1** in the following sequence: P7-P8-P9-P10-P11-P12-(c1-1)-P1-P2-P3-P4-P5-P6-resin, cleaved, cyclized, deprotected and purified as
20 indicated.
Building block (c1-1) is described below.

Examples ex.278-300 (n=12) are shown in *table 7*. The peptides were synthesized starting with the amino acid at position P6 which was grafted to the resin. Starting resins were Fmoc-Arg(Pbf)O-chlorotritylresin, Fmoc-Tyr(Bzl)O-chlorotrityl resin and Fmoc-^DTyr(Bzl)O-chlorotrityl resin which were prepared as described above. The linear peptide was synthesized on solid support according to **procedure 1** in the following sequence: P7-P8-P9-P10-P11-P12-^DPro-Pro-P1-P2-P3-P4-P5-P6-resin, cleaved, cyclized, deprotected and purified as
30 indicated. Analytical HPLC-retention times (RT, in minutes) were determined using a
35 VYDAC 218TP104 (length 25cm) column with *gradient B* (10% CH₃CN + 0.1% TFA and 90% H₂O + 0.1% TFA to 98% CH₃CN + 0.1% TFA and 2% H₂O + 0.1% TFA in 21minutes).

Retention times (minutes) were the following: ex.278 (11.43); ex.279 (11.64); ex.280 (10.57); ex.281 (10.04); ex.282 (10.63); ex.283 (10.00); ex.284 (9.21).

Retention times (minutes) for examples 285-300 were determined with *gradient C*: VYDAC C₁₈- column (length 15cm) ; (8% CH₃CN + 0.1% TFA and 92% H₂O + 0.1% TFA to 62.8% CH₃CN + 0.1% TFA and 37.2% H₂O + 0.1% TFA in 8 minutes to 100% CH₃CN + 0.1% TFA in 9 minutes).

ex.285 (5.37; 5.57)*; ex.286 (5.17); ex.287 (5.0); ex.288 (4.15;4.37)*; ex.289 (4.47; 4.72)*; ex.290 (3.45; 3.72)*; ex.291 (3.65; 3.82)*; ex.292 (4.27); ex.293 (4.10); ex.294 (3.83; 4.13)*; ex.296 (4.38; 4.67)*; ex.297 (4.10; 4.32)*; ex.298 (4.12); ex.299(4.47); ex.300(5.03).

10 * double peaks which show both correct MS and chiral amino acid analysis. At 60° only one peak is observed.

Table 1: Examples ex.1-7 (n=8)

a) %-purity of crude product. All compounds were purified by preparative HPLC-chromatography as indicated. Purities>90%.

Example	SEQ.ID	P1	P2	P3	P4	P5	P6	P7	P8	Template	RT(°) % ^{a)}	MS
1.	SEQ ID NO:1	Tyr	Val	Arg	Arg	Arg	Phe	Leu	Val	DPro ^L Pro	18.6 76	1284.6
2.	SEQ ID NO:2	Tyr	Val	Arg	Lys	Gly	Phe	Leu	Val	DPro ^L Pro	18.8 86	1157.4
3.	SEQ ID NO:3	Trp	Val	Arg	Lys	Gly	Phe	Leu	Trp	DPro ^L Pro	22.0 70	1263.8
4.	SEQ ID NO:4	Tyr	Val	Arg	Arg	Arg	Trp	Leu	Val	DPro ^L Pro	19.1 35	1323.6
5.	SEQ ID NO:5	Tyr	Val	Tyr	Arg	Arg	Phe	Leu	Val	DPro ^L Pro	20.7 81	1287.6
6.	SEQ ID NO:6	Lys	Val	Tyr	Arg	Arg	Phe	Leu	Val	DPro ^L Pro	16.7 75	1256.6
7.	SEQ ID NO:7	Lys	Val	Tyr	Lys	Gly	Phe	Leu	Trp	DPro ^L Pro	19.5 64	1216.5

Table 2: Examples ex.8-29 (n=9)

a) %-purity of crude product. All compounds were purified by preparative HPLC-chromatography as indicated. Purities obtained >90%.

Example	SEQ.ID	P1	P2	P3	P4	P5	P6	P7	P8	P9	Template	RT(°) % ^{a)}	MS
8.	SEQ ID NO:8	Arg	Phe	Leu	Arg	Arg	Arg	Leu	Phe	Arg	D ⁺ Pro ¹ Pro	10.5 35	1495.9
9.	SEQ ID NO:9	Arg	Tyr	Leu	Arg	Arg	Arg	Leu	Tyr	Arg	D ⁺ Pro ¹ Pro	8.8 46	1527.9
10.	SEQ ID NO:10	Arg	Phe	Phe	Arg	Arg	Arg	Leu	Phe	Arg	D ⁺ Pro ¹ Pro	10.0 26	1529.9
11.	SEQ ID NO:11	Arg	Tyr	Tyr	Arg	Arg	Arg	Leu	Tyr	Arg	D ⁺ Pro ¹ Pro	8.0 90	1577.9
12.	SEQ ID NO:12	Leu	Phe	Phe	Arg	Arg	Arg	Leu	Phe	Arg	D ⁺ Pro ¹ Pro	10.2 52	1502.9
13.	SEQ ID NO:13	Leu	Tyr	Tyr	Arg	Arg	Arg	Leu	Tyr	Arg	D ⁺ Pro ¹ Pro	8.4 30	1550.9
14.	SEQ ID NO:14	Arg	Phe	Leu	Phe	Arg	Arg	Leu	Leu	Arg	D ⁺ Pro ¹ Pro	10.1 51	1468.9
15.	SEQ ID NO:15	Arg	Tyr	Leu	Tyr	Arg	Arg	Leu	Leu	Arg	D ⁺ Pro ¹ Pro	8.8 55	1500.9
16.	SEQ ID NO:16	Leu	Phe	Leu	Phe	Arg	Arg	Leu	Phe	Arg	D ⁺ Pro ¹ Pro	9.7 38	1459.9
17.	SEQ ID NO:17	Leu	Tyr	Leu	Tyr	Arg	Arg	Leu	Tyr	Arg	D ⁺ Pro ¹ Pro	11.8 67	1507.9
18.	SEQ ID NO:18	Arg	Phe	Leu	Phe	Arg	Arg	Leu	Phe	Leu	D ⁺ Pro ¹ Pro	10.3 57	1459.9
19.	SEQ ID NO:19	Arg	Tyr	Leu	Tyr	Arg	Arg	Leu	Tyr	Leu	D ⁺ Pro ¹ Pro	11.7 66	1507.9
20.	SEQ ID NO:20	Phe	Leu	Leu	Phe	Arg	Arg	Leu	Phe	Arg	D ⁺ Pro ¹ Pro	9.9 67	1459.9
21.	SEQ ID NO:21	Tyr	Leu	Leu	Tyr	Arg	Arg	Leu	Tyr	Arg	D ⁺ Pro ¹ Pro	11.9 57	1507.9
22.	SEQ ID NO:22	Arg	Leu	Leu	Phe	Arg	Arg	Leu	Phe	Phe	D ⁺ Pro ¹ Pro	10.1 68	1459.9
23.	SEQ ID NO:23	Arg	Leu	Leu	Tyr	Arg	Arg	Leu	Tyr	Tyr	D ⁺ Pro ¹ Pro	11.5 63	1507.9
24.	SEQ ID NO:24	Arg	Phe	Leu	Arg	Arg	Phe	Leu	Phe	Arg	D ⁺ Pro ¹ Pro	8.5 33	1502.9
25.	SEQ ID NO:25	Arg	Phe	Leu	Arg	Arg	Phe	Phe	Leu	Arg	D ⁺ Pro ¹ Pro	10.3 30	1502.9
26.	SEQ ID NO:26	Arg	Tyr	Leu	Arg	Arg	Tyr	Tyr	Leu	Arg	D ⁺ Pro ¹ Pro	12.6 65	1550.9
27.	SEQ ID NO:27	Leu	Tyr	Leu	Arg	Arg	Tyr	Leu	Tyr	Arg	D ⁺ Pro ¹ Pro	10.1 29	1491.8
28.	SEQ ID NO:28	Leu	Leu	Phe	Phe	Arg	Arg	Leu	Phe	Arg	D ⁺ Pro ¹ Pro	12.1 35	1443.8
29.	SEQ ID NO:29	Leu	Leu	Tyr	Tyr	Arg	Arg	Leu	Tyr	Arg	D ⁺ Pro ¹ Pro	10.3 33	1491.8
30.	SEQ ID NO:30	Arg	Leu	Phe	Phe	Arg	Arg	Leu	Phe	Leu	D ⁺ Pro ¹ Pro	12.1 35	1459.9
31.	SEQ ID NO:31	Arg	Leu	Tyr	Tyr	Arg	Arg	Leu	Tyr	Leu	D ⁺ Pro ¹ Pro	10.3 33	1507.8

Table 3: Examples ex.32-58 (n=10)

a) %-purity of crude product. All compounds were purified by preparative HPLC-chromatography as indicated. Purities obtained >90%.

Example	Sequ.ID	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	Template	RT(°) % ^{a)}	MS
32.	SEQ ID NO:32	Arg	Phe	Leu	Phe	Arg	Arg	Arg	Leu	Phe	Arg	D ¹ Pro ¹ Pro	10.2 37	1643.0
33.	SEQ ID NO:33	Arg	Tyr	Leu	Tyr	Arg	Arg	Arg	Leu	Tyr	Arg	D ¹ Pro ¹ Pro	8.3 41	1691.0
34.	SEQ ID NO:34	Arg	Phe	Phe	Phe	Arg	Arg	Arg	Leu	Leu	Arg	D ¹ Pro ¹ Pro	10.1 45	1643.0
35.	SEQ ID NO:35	Arg	Tyr	Tyr	Tyr	Arg	Arg	Arg	Leu	Leu	Arg	D ¹ Pro ¹ Pro	8.87 70	1691.0
36.	SEQ ID NO:36	Arg	Leu	Phe	Phe	Arg	Arg	Arg	Leu	Phe	Arg	D ¹ Pro ¹ Pro	10.4 56	1643.0
37.	SEQ ID NO:37	Leu	Tyr	Leu	Tyr	Arg	Arg	Arg	Leu	Tyr	Arg	D ¹ Pro ¹ Pro	9.6 35	1648.0
38.	SEQ ID NO:38	Arg	Phe	Leu	Phe	Arg	Arg	Arg	Leu	Phe	Leu	D ¹ Pro ¹ Pro	11.1 50	1600.0
39.	SEQ ID NO:39	Arg	Tyr	Leu	Tyr	Arg	Arg	Arg	Leu	Tyr	Leu	D ¹ Pro ¹ Pro	9.81 41	1648.0
40.	SEQ ID NO:40	Leu	Leu	Phe	Phe	Arg	Arg	Arg	Leu	Phe	Arg	D ¹ Pro ¹ Pro	11.8 58	1600.0
41.	SEQ ID NO:41	Arg	Leu	Phe	Phe	Arg	Arg	Arg	Leu	Phe	Leu	D ¹ Pro ¹ Pro	11.6 54	1600.0
42.	SEQ ID NO:42	Leu	Tyr	Tyr	Tyr	Arg	Arg	Arg	Leu	Leu	Arg	D ¹ Pro ¹ Pro	9.9 51	1648.0
43.	SEQ ID NO:43	Arg	Phe	Phe	Phe	Arg	Arg	Arg	Leu	Leu	Leu	D ¹ Pro ¹ Pro	11.3 49	1600.0
44.	SEQ ID NO:44	Arg	Tyr	Tyr	Tyr	Arg	Arg	Arg	Leu	Leu	Leu	D ¹ Pro ¹ Pro	9.9 63	1648.0
45.	SEQ ID NO:45	Arg	Leu	Leu	Phe	Arg	Gly	Arg	Phe	Phe	Arg	D ¹ Pro ¹ Pro	10.6 78	1543.9
46.	SEQ ID NO:46	Arg	Leu	Leu	Tyr	Arg	Gly	Arg	Tyr	Tyr	Arg	D ¹ Pro ¹ Pro	9.1 45	1591.9
47.	SEQ ID NO:47	Arg	Phe	Phe	Phe	Arg	Gly	Arg	Leu	Leu	Arg	D ¹ Pro ¹ Pro	10.4 43	1543.9
48.	SEQ ID NO:48	Arg	Tyr	Tyr	Tyr	Arg	Gly	Arg	Leu	Leu	Arg	D ¹ Pro ¹ Pro	8.8 48	1591.9
49.	SEQ ID NO:49	Leu	Phe	Leu	Phe	Arg	Gly	Arg	Leu	Phe	Arg	D ¹ Pro ¹ Pro	12.4 65	1500.9
50.	SEQ ID NO:50	Leu	Tyr	Leu	Tyr	Arg	Gly	Arg	Leu	Tyr	Arg	D ¹ Pro ¹ Pro	10.3 58	1548.9
51.	SEQ ID NO:51	Arg	Phe	Leu	Phe	Arg	Gly	Arg	Leu	Phe	Leu	D ¹ Pro ¹ Pro	12.3 42	1500.9
52.	SEQ ID NO:52	Arg	Tyr	Leu	Tyr	Arg	Gly	Arg	Leu	Tyr	Leu	D ¹ Pro ¹ Pro	10.6 20	1548.9
53.	SEQ ID NO:53	Leu	Arg	Phe	Phe	Arg	Leu	Arg	Leu	Phe	Arg	D ¹ Pro ¹ Pro	11.9 51	1600.0
54.	SEQ ID NO:54	Leu	Arg	Tyr	Tyr	Arg	Leu	Arg	Leu	Tyr	Arg	D ¹ Pro ¹ Pro	9.9 50	1648.0
55.	SEQ ID NO:55	Leu	Leu	Phe	Phe	Arg	Gly	Arg	Leu	Phe	Arg	D ¹ Pro ¹ Pro	12.5 50	1500.9
56.	SEQ ID NO:56	Leu	Leu	Tyr	Tyr	Arg	Gly	Arg	Leu	Tyr	Arg	D ¹ Pro ¹ Pro	10.1 38	1548.9
57.	SEQ ID NO:57	Arg	Phe	Leu	Phe	Arg	Gly	Arg	Phe	Arg	Leu	D ¹ Pro ¹ Pro	11.3 57	1543.9
58.	SEQ ID NO:58	Arg	Tyr	Leu	Tyr	Arg	Gly	Arg	Tyr	Arg	Leu	D ¹ Pro ¹ Pro	10.8 56	1591.9

Table 4: Examples ex.59-70 (n=11)

a) %-purity of crude product. All compounds were purified by preparative HPLC-chromatography as indicated. Purities >90%.

Example	SEQ.ID	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	Template	RT(')	%	MS
59.	SEQ ID NO:59	Arg	Leu	Phe	Leu	Arg	Arg	Arg	Phe	Phe	Arg	Leu	DPro ¹ Pro	11.1	75	1756.2
60.	SEQ ID NO:60	Arg	Leu	Tyr	Leu	Arg	Arg	Arg	Tyr	Tyr	Arg	Leu	DPro ¹ Pro	9.5	28	1804.2
61.	SEQ ID NO:61	Leu	Leu	Phe	Leu	Arg	Arg	Arg	Phe	Phe	Arg	Arg	DPro ¹ Pro	10.8	65	1756.2
62.	SEQ ID NO:62	Arg	Leu	Phe	Leu	Arg	Arg	Arg	Leu	Phe	Arg	Phe	DPro ¹ Pro	11.3	57	1756.2
63.	SEQ ID NO:63	Phe	Leu	Phe	Leu	Arg	Arg	Arg	Leu	Phe	Arg	Arg	DPro ¹ Pro	11.1	76	1756.2
64.	SEQ ID NO:64	Tyr	Leu	Tyr	Leu	Arg	Arg	Arg	Leu	Tyr	Arg	Arg	DPro ¹ Pro	9.5	70	1804.2
65.	SEQ ID NO:65	Arg	Arg	Phe	Leu	Arg	Gly	Arg	Phe	Phe	Leu	Arg	DPro ¹ Pro	9.8	36	1700.1
66.	SEQ ID NO:66	Leu	Leu	Tyr	Tyr	Arg	Arg	Leu	Tyr	Tyr	Arg	Arg	DPro ¹ Pro	9.9	47	1811.2
67.	SEQ ID NO:67	Leu	Tyr	Leu	Tyr	Arg	Arg	Tyr	Leu	Tyr	Arg	Arg	DPro ¹ Pro	9.9	47	1811.2
68.	SEQ ID NO:68	Arg	Arg	Phe	Phe	Arg	Arg	Leu	Phe	Phe	Leu	Leu	DPro ¹ Pro	12.4	46	1747.2
69.	SEQ ID NO:69	Arg	Leu	Tyr	Tyr	Arg	Arg	Leu	Tyr	Tyr	Arg	Leu	DPro ¹ Pro	9.9	51	1811.2
70.	SEQ ID NO:70	Arg	Leu	Phe	Phe	Arg	Gly	Arg	Phe	Phe	Arg	Leu	DPro ¹ Pro	10.5	26	1691.1

Table 5: Examples ex.71-84 (n=14)

a) %-purity of crude product. All compounds were purified by preparative HPLC-chromatography. Purities>90%.

Example	SEQ.ID	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14	Template	RT(°)	%	MS
71.	SEQ ID NO:71	Arg	Tyr	Leu	Leu	Tyr	Arg	Arg	Tyr	Leu	Leu	Leu	Tyr	Arg	Arg	DPro ^L Pro	9.4	48	2236.7
72.	SEQ ID NO:72	Arg	Leu	Leu	Tyr	Tyr	Arg	Arg	Tyr	Leu	Leu	Leu	Tyr	Arg	Arg	DPro ^L Pro	9.4	29	2236.7
73.	SEQ ID NO:73	Arg	Leu	Leu	Leu	Tyr	Arg	Arg	Tyr	Leu	Leu	Tyr	Tyr	Arg	Arg	DPro ^L Pro	9.4	50	2236.7
74.	SEQ ID NO:74	Arg	Phe	Leu	Phe	Leu	Arg	Arg	Phe	Phe	Phe	Leu	Phe	Arg	Arg	DPro ^L Pro	10.9	78	2206.7
75.	SEQ ID NO:75	Arg	Tyr	Leu	Tyr	Leu	Arg	Arg	Tyr	Tyr	Tyr	Leu	Tyr	Arg	Arg	DPro ^L Pro	9.1	51	2286.7
76.	SEQ ID NO:76	Arg	Phe	Leu	Phe	Leu	Arg	Arg	Phe	Leu	Leu	Phe	Leu	Arg	Arg	DPro ^L Pro	10.6	79	2172.7
77.	SEQ ID NO:77	Arg	Tyr	Leu	Tyr	Leu	Arg	Arg	Tyr	Leu	Leu	Tyr	Leu	Arg	Arg	DPro ^L Pro	9.1	53	2236.7
78.	SEQ ID NO:78	Arg	Arg	Leu	Leu	Leu	Arg	Arg	Phe	Leu	Leu	Leu	Phe	Arg	Arg	DPro ^L Pro	11.0	42	2172.7
79.	SEQ ID NO:79	Arg	Arg	Leu	Leu	Tyr	Arg	Arg	Tyr	Leu	Leu	Leu	Tyr	Tyr	Arg	DPro ^L Pro	9.4	91	2236.7
80.	SEQ ID NO:80	Arg	Arg	Leu	Tyr	Tyr	Arg	Arg	Tyr	Leu	Leu	Leu	Tyr	Tyr	Arg	DPro ^L Pro	9.3	72	2286.7
81.	SEQ ID NO:81	Arg	Arg	Leu	Leu	Tyr	Arg	Arg	Tyr	Leu	Leu	Tyr	Tyr	Leu	Arg	DPro ^L Pro	9.5	65	2236.7
82.	SEQ ID NO:82	Arg	Arg	Leu	Phe	Leu	Arg	Arg	Phe	Phe	Phe	Leu	Phe	Phe	Arg	DPro ^L Pro	11.1	34	2206.7
83.	SEQ ID NO:83	Arg	Arg	Leu	Tyr	Leu	Arg	Arg	Tyr	Tyr	Tyr	Leu	Tyr	Tyr	Arg	DPro ^L Pro	9.3	89	2286.7
84.	SEQ ID NO:84	Arg	Arg	Leu	Tyr	Leu	Arg	Arg	Tyr	Leu	Leu	Tyr	Leu	Tyr	Arg	DPro ^L Pro	9.3	47	2236.7

Table 6: Examples ex.85-95 (n=16)

a) %-purity of crude product. All compounds were purified by preparative HPLC-chromatography. Purities>90%.

Example	Seq.ID	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14	P15	P16	Template	RT(')	%	MS
85.	SEQ ID NO:85	Lys	Arg	Leu	Lys	Tyr	Val	Arg	Arg	Arg	Trp	Leu	Val	Lys	Val	Leu	Arg	DPro ^L -Pro	13.7	70	2346.0
86.	SEQ ID NO:86	Lys	Arg	Leu	Lys	Tyr	Val	Arg	Arg	Gly	Trp	Leu	Val	Lys	Val	Leu	Arg	DPro ^L -Pro	13.9	38	2246.8
87.	SEQ ID NO:87	Lys	Arg	Leu	Lys	Tyr	Trp	Arg	Arg	Arg	Trp	Tyr	Val	Lys	Val	Leu	Arg	DPro ^L -Pro	13.6	34	2483.1
88.	SEQ ID NO:88	Lys	Arg	Leu	Tyr	Tyr	Trp	Arg	Arg	Arg	Trp	Tyr	Val	Phe	Val	Leu	Arg	DPro ^L -Pro	14.3	35	2537.1
89.	SEQ ID NO:89	Lys	Arg	Leu	Lys	Tyr	Trp	Arg	Arg	Gly	Trp	Tyr	Val	Lys	Val	Leu	Arg	DPro ^L -Pro	13.7	27	2383.9
90.	SEQ ID NO:90	Lys	Arg	Leu	Tyr	Tyr	Trp	Arg	Arg	Gly	Trp	Tyr	Val	Phe	Val	Leu	Arg	DPro ^L -Pro	14.6	39	2437.9
91.	SEQ ID NO:91	Lys	Arg	Leu	Tyr	Tyr	Trp	Arg	Arg	Arg	Trp	Lys	Val	Phe	Val	Leu	Arg	DPro ^L -Pro	13.9	22	2402.1
92.	SEQ ID NO:92	Lys	Arg	Leu	Lys	Tyr	Trp	Arg	Arg	Gly	Trp	Lys	Val	Lys	Val	Leu	Arg	DPro ^L -Pro	13.4	26	2348.9
93.	SEQ ID NO:93	Tyr	Lys	Leu	Arg	Leu	Lys	Tyr	Arg	Arg	Trp	Lys	Tyr	Arg	Val	Lys	Phe	DPro ^L -Pro	12.5	34	2402.1
94.	SEQ ID NO:94	Tyr	Lys	Leu	Gln	Leu	Lys	Trp	Arg	Arg	Phe	Lys	Tyr	Gln	Val	Lys	Phe	DPro ^L -Pro	12.1	21	2348.9
95.	SEQ ID NO:95	Tyr	Lys	Leu	Gln	Leu	Gln	Lys	Lys	Gly	Trp	Gln	Tyr	Gln	Val	Lys	Phe	DPro ^L -Pro	11.1	84	2383.9

Table 7: Examples ex.96-128 (n=12);
a) %-purity of crude product. Purities of all compounds after prep. HPLC>90%.

Example	Seq.ID	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	Template	RT(') %	MS
96.	SEQ ID NO:96	Leu	Arg	Leu	Val	Tyr	Lys	Gly	Phe	Leu	Tyr	Arg	Val	D ^{Pro} -Pro	21.6	1703.1
97.	SEQ ID NO:97	Leu	Arg	Phe	Val	Tyr	Lys	Gly	Phe	Leu	Tyr	Arg	Val	D ^{Pro} -Pro	21.6	1737.1
98.	SEQ ID NO:98	Leu	Arg	Thr	Val	Tyr	Lys	Gly	Phe	Leu	Tyr	Arg	Val	D ^{Pro} -Pro	20.0	1691.1
99.	SEQ ID NO:99	Leu	Arg	Lys	Val	Arg	Lys	Gly	Arg	Leu	Tyr	Arg	Val	D ^{Pro} -Pro	15.7	1720.2
100.	SEQ ID NO:100	Leu	Arg	Lys	Trp	Tyr	Lys	Gly	Phe	Trp	Tyr	Arg	Val	D ^{Pro} -Pro	17.6	1878.3
101.	SEQ ID NO:101	Leu	Arg	Lys	Val	Tyr	Arg	Gly	Phe	Leu	Tyr	Arg	Val	D ^{Pro} -Pro	17.8	1845.3
102.	SEQ ID NO:102	Leu	Lys	Lys	Val	Tyr	Arg	Arg	Phe	Leu	Lys	Lys	Val	D ^{Pro} -Pro	15.9	1754.3
103.	SEQ ID NO:103	Leu	Arg	Leu	Lys	Tyr	Arg	Arg	Phe	Lys	Tyr	Arg	Val	D ^{Pro} -Pro	20.5	1874.3
104.	SEQ ID NO:104	Leu	Arg	Leu	Glu	Tyr	Arg	Arg	Phe	Glu	Tyr	Arg	Val	D ^{Pro} -Pro	21.5	1876.2
105.	SEQ ID NO:105	Leu	Arg	Leu	Gln	Tyr	Arg	Arg	Phe	Gln	Tyr	Arg	Val	D ^{Pro} -Pro	21.5	1874.2
106.	SEQ ID NO:106	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	D ^{Pro} -Pro	18.1	1879.7
107.	SEQ ID NO:107	Leu	Arg	Leu	Lys	Trp	Arg	Arg	Lys	Lys	Tyr	Arg	Val	D ^{Pro} -Pro	20.2	1879.7
108.	SEQ ID NO:108	Leu	Arg	Trp	Lys	Tyr	Arg	Arg	Phe	Lys	Tyr	Arg	Val	D ^{Pro} -Pro	20.9	1948.7
109.	SEQ ID NO:109	Lys	Val	Arg	Phe	Arg	Arg	Arg	Lys	Leu	Lys	Leu	Arg	D ^{Pro} -Pro	15.7	1833.7
110.	SEQ ID NO:110	Leu	Arg	Leu	Gln	Tyr	Arg	Arg	Trp	Gln	Tyr	Arg	Val	D ^{Pro} -Pro	21.9	1913.3
111.	SEQ ID NO:111	Leu	Arg	Leu	Gln	Trp	Arg	Arg	Phe	Gln	Tyr	Arg	Val	D ^{Pro} -Pro	22.6	1897.3
112.	SEQ ID NO:112	Leu	Arg	Leu	Gln	Lys	Arg	Arg	Trp	Gln	Tyr	Arg	Val	D ^{Pro} -Pro	18.9	1878.3
113.	SEQ ID NO:113	Leu	Arg	Leu	Gln	Trp	Arg	Arg	Lys	Gln	Tyr	Arg	Val	D ^{Pro} -Pro	21.2	1878.3
114.	SEQ ID NO:114	Phe	Arg	Leu	Gln	Tyr	Arg	Arg	Phe	Gln	Tyr	Arg	Val	D ^{Pro} -Pro	22.3	1908.3
115.	SEQ ID NO:115	Leu	Arg	Leu	Gln	Tyr	Arg	Arg	Phe	Gln	Tyr	Arg	Phe	D ^{Pro} -Pro	22.4	1908.3
116.	SEQ ID NO:116	Phe	Arg	Leu	Gln	Tyr	Arg	Arg	Phe	Gln	Tyr	Arg	Phe	D ^{Pro} -Pro	22.9	1956.3
117.	SEQ ID NO:117	Leu	Arg	Leu	Gln	Tyr	Arg	Arg	Phe	Gln	Trp	Arg	Val	D ^{Pro} -Pro	22.7	1897.3
118.	SEQ ID NO:118	Leu	Arg	Trp	Gln	Tyr	Arg	Arg	Phe	Gln	Tyr	Arg	Val	D ^{Pro} -Pro	21.9	1947.3
119.	SEQ ID NO:119	Gln	Val	Arg	Phe	Arg	Arg	Arg	Lys	Leu	Gln	Leu	Arg	D ^{Pro} -Pro	17.2	1831.3
120.	SEQ ID NO:120	Phe	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	D ^{Pro} -Pro	10.5	1912.4
121.	SEQ ID NO:121	Cha	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	D ^{Pro} -Pro	10.6	1918.4
122.	SEQ ID NO:122	hPhe	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	D ^{Pro} -Pro	9.6	1926.4
123.	SEQ ID NO:123	2Nal	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	D ^{Pro} -Pro	9.6	1962.4
124.	SEQ ID NO:124	1Nal	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	D ^{Pro} -Pro	11.8	1962.4
125.	SEQ ID NO:125	Nle	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	D ^{Pro} -Pro	10.3	1878.4
126.	SEQ ID NO:126	Leu	Arg	Phe	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	D ^{Pro} -Pro	10.6	1912.4
127.	SEQ ID NO:127	Leu	Arg	Cha	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	D ^{Pro} -Pro	10.8	1918.4
128.	SEQ ID NO:128	Leu	Arg	Y(ozl)Lys	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	D ^{Pro} -Pro	11.5	2018.5

Table 7 (continued): Examples ex.129-161 (n=12)

Example	SEQ.ID	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	Template	RT(')	%	MS
129.	SEQ ID NO:129	Leu	Arg	Trp	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro ^L Pro	10.5	41	1951.4
130.	SEQ ID NO:130	Leu	Arg	hPhe	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro ^L Pro	10.6	32	1926.4
131.	SEQ ID NO:131	Leu	Arg	2Nal	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro ^L Pro	11.0	42	1962.4
132.	SEQ ID NO:132	Leu	Arg	1Nal	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro ^L Pro	10.9	43	1962.4
133.	SEQ ID NO:133	Leu	Arg	Val	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro ^L Pro	10.0	47	1864.3
134.	SEQ ID NO:134	Leu	Arg	Ile	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro ^L Pro	10.3	34	1878.4
135.	SEQ ID NO:135	Leu	Arg	Nle	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro ^L Pro	10.3	90	1878.4
136.	SEQ ID NO:136	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Arg	Val	DPro ^L Pro	9.9	48	1855.3
137.	SEQ ID NO:137	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Y(Bzl)Lys	Lys	Tyr	Arg	Val	DPro ^L Pro	11.0	33	1945.4
138.	SEQ ID NO:138	Leu	Arg	Leu	Lys	Lys	Arg	Arg	hPhe	Lys	Tyr	Arg	Val	DPro ^L Pro	10.3	52	1833.3
139.	SEQ ID NO:139	Leu	Arg	Leu	Lys	Lys	Arg	Arg	2Nal	Lys	Tyr	Arg	Val	DPro ^L Pro	10.5	53	1889.4
140.	SEQ ID NO:140	Leu	Arg	Leu	Lys	Lys	Arg	Arg	1Nal	Lys	Tyr	Arg	Val	DPro ^L Pro	10.5	34	1889.4
141.	SEQ ID NO:141	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Val	Lys	Tyr	Arg	Val	DPro ^L Pro	9.9	49	1889.4
142.	SEQ ID NO:142	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Ile	Lys	Tyr	Arg	Val	DPro ^L Pro	10.0	32	1791.3
143.	SEQ ID NO:143	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Leu	Lys	Tyr	Arg	Val	DPro ^L Pro	10.1	46	1805.3
144.	SEQ ID NO:144	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Nle	Lys	Tyr	Arg	Val	DPro ^L Pro	10.1	43	1805.3
145.	SEQ ID NO:145	Leu	Arg	Leu	Lys	Lys	Arg	Arg	His	Lys	Tyr	Arg	Val	DPro ^L Pro	9.8	56	1829.3
146.	SEQ ID NO:146	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Phe	Arg	Val	DPro ^L Pro	10.9	45	1862.3
147.	SEQ ID NO:147	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Y(Bzl)Arg	Arg	Val	DPro ^L Pro	11.4	15	1968.5
148.	SEQ ID NO:148	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Trp	Arg	Val	DPro ^L Pro	10.8	56	1901.4
149.	SEQ ID NO:149	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	hPhe	Arg	Val	DPro ^L Pro	11.3	32	1876.4
150.	SEQ ID NO:150	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	1Nal	Arg	Val	DPro ^L Pro	11.6	24	1912.4
151.	SEQ ID NO:151	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Val	Arg	Val	DPro ^L Pro	10.6	48	1814.3
152.	SEQ ID NO:152	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Ile	Arg	Val	DPro ^L Pro	10.9	40	1828.3
153.	SEQ ID NO:153	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Leu	Arg	Val	DPro ^L Pro	10.7	18	1828.3
154.	SEQ ID NO:154	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Nle	Arg	Val	DPro ^L Pro	11.2	40	1828.3
155.	SEQ ID NO:155	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Phe	DPro ^L Pro	10.6	35	1926.4
156.	SEQ ID NO:156	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Cha	DPro ^L Pro	11.2	60	1932.5
157.	SEQ ID NO:157	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Y(Bzl)	DPro ^L Pro	11.7	37	2032.5
158.	SEQ ID NO:158	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Trp	DPro ^L Pro	10.4	69	1965.4
159.	SEQ ID NO:159	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	hPhe	DPro ^L Pro	10.8	95	1940.4
160.	SEQ ID NO:160	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	2Nal	DPro ^L Pro	11.2	30	1976.5
161.	SEQ ID NO:161	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	1Nal	DPro ^L Pro	11.3	89	1976.5

Table 7 (continued): Examples ex.162-194 (n=12)

Example	SEQ ID NO:	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	Template	RT(°)	%	MS
162.	SEQ ID NO:162	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Ile	DPro ¹ Pro	10.5	56	1892.4
163.	SEQ ID NO:163	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Nle	DPro ¹ Pro	10.5	91	1892.4
164.	SEQ ID NO:164	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	His	DPro ¹ Pro	8.6	88	1916.4
165.	SEQ ID NO:165	Leu	Trp	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro ¹ Pro	10.4	55	1908.4
166.	SEQ ID NO:166	Leu	Leu	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro ¹ Pro	10.6	88	1835.3
167.	SEQ ID NO:167	Leu	Thr	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro ¹ Pro	10.4	94	1823.3
168.	SEQ ID NO:168	Leu	Gln	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro ¹ Pro	10.4	55	1850.3
169.	SEQ ID NO:169	Leu	Arg	Leu	Leu	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro ¹ Pro	10.9	62	1863.3
170.	SEQ ID NO:170	Leu	Arg	Leu	Arg	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro ¹ Pro	10.3	45	1906.4
171.	SEQ ID NO:171	Leu	Arg	Leu	Thr	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro ¹ Pro	10.4	94	1851.3
172.	SEQ ID NO:172	Leu	Arg	Leu	Gln	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro ¹ Pro	10.3	76	1878.3
173.	SEQ ID NO:173	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro ¹ Pro	11.9	43	1863.3
174.	SEQ ID NO:174	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro ¹ Pro	10.5	53	1887.3
175.	SEQ ID NO:175	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro ¹ Pro	10.4	37	1906.4
176.	SEQ ID NO:176	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro ¹ Pro	11.4	45	1851.3
177.	SEQ ID NO:177	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro ¹ Pro	10.8	58	1835.3
178.	SEQ ID NO:178	Leu	Arg	Leu	Lys	Lys	His	Arg	Trp	Lys	Tyr	Arg	Val	DPro ¹ Pro	10.2	46	1859.3
179.	SEQ ID NO:179	Leu	Arg	Leu	Lys	Lys	Lys	Arg	Trp	Lys	Tyr	Arg	Val	DPro ¹ Pro	10.3	53	1850.3
180.	SEQ ID NO:180	Leu	Arg	Leu	Lys	Lys	Thr	Arg	Trp	Lys	Tyr	Arg	Val	DPro ¹ Pro	10.4	82	1823.3
181.	SEQ ID NO:181	Leu	Arg	Leu	Lys	Lys	Gln	Arg	Trp	Lys	Tyr	Arg	Val	DPro ¹ Pro	10.4	36	1850.3
182.	SEQ ID NO:182	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro ¹ Pro	10.8	70	1908.4
183.	SEQ ID NO:183	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro ¹ Pro	10.3	74	1859.3
184.	SEQ ID NO:184	Leu	Arg	Leu	Lys	Lys	Arg	Lys	Trp	Lys	Tyr	Arg	Val	DPro ¹ Pro	10.2	50	1850.3
185.	SEQ ID NO:185	Bip	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro ¹ Pro	11.4	39	1988.5
186.	SEQ ID NO:186	4CIPheArg	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro ¹ Pro	11.1	53	1946.8
187.	SEQ ID NO:187	AmPheArg	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro ¹ Pro	8.6	83	1927.4
188.	SEQ ID NO:188	S(Bzl)Arg	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro ¹ Pro	10.4	66	1942.4
189.	SEQ ID NO:189	T(Bzl)Arg	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro ¹ Pro	10.8	51	1956.4
190.	SEQ ID NO:190	Om	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro ¹ Pro	8.4	84	1879.3
191.	SEQ ID NO:191	Leu	Arg	Bip	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro ¹ Pro	11.3	39	1988.5
192.	SEQ ID NO:192	Leu	Arg	4CIPheLys	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro ¹ Pro	10.9	50	1946.8
193.	SEQ ID NO:193	Leu	Arg	AmPheLys	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro ¹ Pro	9.2	82	1927.4
194.	SEQ ID NO:194	Leu	Arg	S(Bzl)Lys	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro ¹ Pro	10.7	80	1942.4

Table 7 (continued): Examples ex.195-227 (n=12)

Example	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	Template	RT(°)	%	MS
195.	Leu	Arg	T(Bzl)	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Arg	Val	D ^{Pro} -Pro	10.7	37	1956.4
196.	Leu	Arg	Om	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Arg	Val	D ^{Pro} -Pro	9.2	48	1879.3
197.	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Bip	Lys	Tyr	Arg	Val	D ^{Pro} -Pro	10.8	57	1915.4
198.	Leu	Arg	Leu	Lys	Lys	Arg	Arg	4CIPheLys	Lys	Tyr	Arg	Val	D ^{Pro} -Pro	10.4	49	1873.8
199.	Leu	Arg	Leu	Lys	Lys	Arg	Arg	AmPheLys	Lys	Tyr	Arg	Val	D ^{Pro} -Pro	9.8	43	1854.3
200.	Leu	Arg	Leu	Lys	Lys	Arg	Arg	S(Bzl)	Lys	Tyr	Arg	Val	D ^{Pro} -Pro	10.3	48	1869.3
201.	Leu	Arg	Leu	Lys	Lys	Arg	Arg	T(Bzl)	Lys	Tyr	Arg	Val	D ^{Pro} -Pro	10.2	87	1883.4
202.	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Om	Lys	Tyr	Arg	Val	D ^{Pro} -Pro	9.7	31	1806.3
203.	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Bip	Arg	Val	D ^{Pro} -Pro	11.6	46	1938.5
204.	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	4CIPheArg	Val	Val	D ^{Pro} -Pro	11.21	48	1896.8
205.	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	S(Bzl)	Arg	Val	D ^{Pro} -Pro	11.5	32	1892.4
206.	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	T(Bzl)	Arg	Val	D ^{Pro} -Pro	11.5	36	1906.4
207.	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Om	Arg	Val	D ^{Pro} -Pro	9.4	49	1829.3
208.	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Arg	Bip	D ^{Pro} -Pro	11.7	37	2002.5
209.	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Arg	4CIPhe	D ^{Pro} -Pro	11.0	32	1960.8
210.	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Arg	AmPhe	D ^{Pro} -Pro	8.6	88	1941.4
211.	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Arg	T(Bzl)	D ^{Pro} -Pro	10.9	51	1970.5
212.	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Arg	Om	D ^{Pro} -Pro	8.3	75	1893.4
213.	Leu	Om	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Arg	Val	D ^{Pro} -Pro	10.3	63	1836.3
214.	Leu	Arg	Leu	Om	Lys	Arg	Arg	Tyr	Lys	Tyr	Arg	Val	D ^{Pro} -Pro	10.4	44	1864.3
215.	Leu	Arg	Leu	Lys	Om	Arg	Arg	Tyr	Lys	Tyr	Arg	Val	D ^{Pro} -Pro	10.2	44	1864.3
216.	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Arg	Val	D ^{Pro} -Pro	10.2	44	1836.3
217.	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Arg	Val	D ^{Pro} -Pro	10.3	40	1864.3
218.	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Arg	Val	D ^{Pro} -Pro	10.2	92	1836.3
219.	Leu	Arg	Leu	Lys	Lys	Arg	Gln	Tyr	Lys	Tyr	Arg	Val	D ^{Pro} -Pro	10.4	92	1850.3
220.	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Arg	Val	D ^{Pro} -Pro	10.5	88	1913.4
221.	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	His	Tyr	Arg	Val	D ^{Pro} -Pro	10.4	49	1887.3
222.	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Arg	Tyr	Arg	Val	D ^{Pro} -Pro	10.3	53	1906.4
223.	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Thr	Tyr	Arg	Val	D ^{Pro} -Pro	10.5	84	1851.3
224.	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Gln	Tyr	Arg	Val	D ^{Pro} -Pro	10.5	52	1878.3
225.	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Tyr	Val	D ^{Pro} -Pro	10.6	54	1885.3
226.	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Tyr	Val	D ^{Pro} -Pro	10.9	47	1908.4
227.	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Bip	Lys	Bip	Arg	Val	D ^{Pro} -Pro	12.3	50	1975.5

Table 7 (continued): Examples ex.228-255 (n=12)

Example	SEQ ID NO:	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	Template	RT(°) %	MS
228.	SEQ ID NO:228	Leu	Arg	Leu	Arg	Lys	Arg	Arg	Bip	Lys	Tyr	Arg	Val	DPro ¹ Pro	10.9	1943.4
229.	SEQ ID NO:229	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Bip	Arg	Tyr	Arg	Val	DPro ¹ Pro	10.9	1943.4
230.	SEQ ID NO:230	Leu	Trp	Leu	Lys	Lys	Arg	Arg	Bip	Lys	Tyr	Arg	Val	DPro ¹ Pro	11.0	1945.4
231.	SEQ ID NO:231	Leu	Trp	Leu	Arg	Lys	Arg	Arg	Bip	Lys	Tyr	Arg	Val	DPro ¹ Pro	11.0	1973.5
232.	SEQ ID NO:232	Leu	Trp	Leu	Lys	Lys	Arg	Arg	Bip	Arg	Tyr	Arg	Val	DPro ¹ Pro	11.0	1973.5
233.	SEQ ID NO:233	Leu	Trp	Leu	Arg	Lys	Arg	Arg	Bip	Lys	Bip	Arg	Val	DPro ¹ Pro	12.4	2033.6
234.	SEQ ID NO:234	Leu	Trp	Leu	Lys	Lys	Arg	Arg	Bip	Arg	Bip	Arg	Val	DPro ¹ Pro	12.4	2033.6
235.	SEQ ID NO:235	Leu	Trp	Leu	Arg	Lys	Arg	Arg	Bip	Arg	Bip	Arg	Bip	DPro ¹ Pro	11.6	2185.7
236.	SEQ ID NO:236	4CIPheArg	4CIPheArg	Leu	Lys	Lys	Arg	Arg	Bip	Lys	Tyr	Arg	Val	DPro ¹ Pro	10.7	1983.9
237.	SEQ ID NO:237	4CIPheArg	4CIPheArg	Leu	Lys	Lys	Arg	Arg	Bip	Lys	Bip	Arg	Val	DPro ¹ Pro	13.0	2043.9
238.	SEQ ID NO:238	4CIPheArg	4CIPheArg	Leu	Lys	Lys	Arg	Arg	Bip	Lys	Tyr	Arg	Bip	DPro ¹ Pro	12.9	2108.0
239.	SEQ ID NO:239	4CIPheArg	4CIPheArg	Leu	Lys	Lys	Arg	Arg	Bip	Lys	Bip	Arg	Bip	DPro ¹ Pro	12.6	2168.1
240.	SEQ ID NO:240	4CIPheArg	4CIPheArg	Leu	Arg	Lys	Arg	Arg	Bip	Lys	Tyr	Arg	Val	DPro ¹ Pro	11.7	2011.9
241.	SEQ ID NO:241	4CIPheArg	4CIPheArg	Leu	Lys	Lys	Arg	Arg	Bip	Arg	Tyr	Arg	Val	DPro ¹ Pro	11.7	2011.9
242.	SEQ ID NO:242	4CIPheTrp	4CIPheTrp	Leu	Lys	Lys	Arg	Arg	Bip	Lys	Tyr	Arg	Val	DPro ¹ Pro	11.8	2013.9
243.	SEQ ID NO:243	4CIPheTrp	4CIPheTrp	Leu	Arg	Lys	Arg	Arg	Bip	Lys	Tyr	Arg	Val	DPro ¹ Pro	11.9	2041.9
244.	SEQ ID NO:244	4CIPheTrp	4CIPheTrp	Leu	Lys	Lys	Arg	Arg	Bip	Arg	Tyr	Arg	Val	DPro ¹ Pro	11.9	2041.9
245.	SEQ ID NO:245	4CIPheTrp	4CIPheTrp	Leu	Arg	Lys	Arg	Arg	Bip	Lys	Bip	Arg	Val	DPro ¹ Pro	13.2	2102.0
246.	SEQ ID NO:246	4CIPheTrp	4CIPheTrp	Leu	Lys	Lys	Arg	Arg	Bip	Arg	Bip	Arg	Val	DPro ¹ Pro	13.2	2102.0
247.	SEQ ID NO:247	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro-Gly	9.5	1838.3
248.	SEQ ID NO:248	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro-Arg	9.3	1937.4
249.	SEQ ID NO:249	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro-Tyr	9.9	1944.4
250.	SEQ ID NO:250	Leu	Arg	Leu	Arg	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro-Phe	10.7	1928.4
251.	SEQ ID NO:251	Leu	Arg	Leu	Arg	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro-Trp	10.7	1967.5
252.	SEQ ID NO:252	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro-Leu	10.5	1894.4
253.	SEQ ID NO:253	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro-Ile	10.4	1894.4
254.	SEQ ID NO:254	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro-Cha	11.2	1934.5
255.	SEQ ID NO:255	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Arg	Val	DPro-2Nal	11.4	1978.5

Table 7 (continued): Examples ex.256-286 (n=12)

All products were purified by preparative HPLC-chromatography. Purities >90%.

Example SEQ.ID	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	Template	MS
256.	SEQ ID NO:256	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Arg	Val	DPro-A8'-1 1990.5
257.	SEQ ID NO:257	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Arg	Val	DPro-A8'-2 2018.3
258.	SEQ ID NO:258	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Arg	Val	DPro-A8'-3 2086.4
259.	SEQ ID NO:259	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Arg	Val	DPro-A8'-4 2086.4
260.	SEQ ID NO:260	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Arg	Val	DPro-A8'-5 1978.3
261.	SEQ ID NO:261	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Arg	Val	DPro-A8'-6 2023.3
262.	SEQ ID NO:262	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Arg	Val	DPro-A8'-7 1934.3
263.	SEQ ID NO:263	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Arg	Val	DPro-A8'-8 1948.2
264.	SEQ ID NO:264	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Arg	Val	DPro-A8'-9 1962.2
265.	SEQ ID NO:265	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Arg	Val	DPro-A8'-10 1976.3
266.	SEQ ID NO:266	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Arg	Val	DPro-A8'-11 1962.2
267.	SEQ ID NO:267	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Arg	Val	DPro-A8'-12 2002.3
268.	SEQ ID NO:268	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Arg	Val	DPro-A8'-13 2016.3
269.	SEQ ID NO:269	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Arg	Val	DPro-A8'-14 1976.3
270.	SEQ ID NO:270	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Arg	Val	DPro-A8'-15 1996.2
271.	SEQ ID NO:271	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Arg	Val	DPro-A8'-16 2011.4
272.	SEQ ID NO:272	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Arg	Val	DPro-A8'-17 2049.3
273.	SEQ ID NO:273	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Arg	Val	DPro-A8'-18 2063.4
274.	SEQ ID NO:274	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Arg	Val	DPro-A8'-19 2072.3
275.	SEQ ID NO:275	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Arg	Val	DPro-A8'-20 2046.4
276.	SEQ ID NO:276	Leu	Arg	Leu	Lys	Lys	Gly	Arg	Tyr	Lys	Tyr	Arg	Val	DPro ^L Pro 1779.2
277.	SEQ ID NO:277	Leu	Arg	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Arg	Val	(cl)-1 2023.2
278.	SEQ ID NO:278	Leu	Tyr	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Tyr	Val	DPro ^L Pro 1892.3
279.	SEQ ID NO:279	Leu	Tyr	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Tyr	Val	DPro ^L Pro 1915.4
280.	SEQ ID NO:280	Arg	Tyr	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Tyr	Val	DPro ^L Pro 1981.4
281.	SEQ ID NO:281	Arg	Tyr	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Tyr	Val	DPro ^L Pro 1958.4
282.	SEQ ID NO:282	Leu	Tyr	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Tyr	Arg	DPro ^L Pro 1995.5
283.	SEQ ID NO:283	Leu	Tyr	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Tyr	Arg	DPro ^L Pro 1972.4
284.	SEQ ID NO:284	Arg	Tyr	Leu	Lys	Lys	Arg	Arg	Tyr	Lys	Tyr	Tyr	Arg	DPro ^L Pro 2015.5
285.	SEQ ID NO:285	Leu	Arg	Leu	Lys	Lys	Y(Bzl)Arg	Arg	Tyr	Lys	Tyr	Arg	Val	DPro ^L Pro 1975.5
286.	SEQ ID NO:286	Leu	Arg	Leu	Lys	Lys	DY(Bzl)Arg	Arg	Tyr	Lys	Tyr	Arg	Val	DPro ^L Pro 1975.5

Table 7 (continued): Examples ex.287-300 (n=12)

All products were purified by preparative HPLC-chromatography. Purities >90%.

Example	SEQ.ID	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	Tcmplate	MS
287.	SEQ ID NO:287	Bip	Trp	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Tyr	Arg	DPro ^L Pro	2082.6
288.	SEQ ID NO:288	Thr	Trp	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Tyr	Arg	DPro ^L Pro	1960.4
289.	SEQ ID NO:289	Arg	Bip	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Tyr	Arg	DPro ^L Pro	2052.5
290.	SEQ ID NO:290	Arg	Thr	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Tyr	Arg	DPro ^L Pro	1930.4
291.	SEQ ID NO:291	Arg	Trp	Thr	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Tyr	Arg	DPro ^L Pro	2003.4
292.	SEQ ID NO:292	Arg	Trp	Leu	Arg	Lys	Arg	Arg	Trp	Lys	Tyr	Tyr	Arg	DPro ^L Pro	2043.5
293.	SEQ ID NO:293	Arg	Trp	Leu	Gln	Lys	Arg	Arg	Trp	Lys	Tyr	Tyr	Arg	DPro ^L Pro	2015.4
294.	SEQ ID NO:294	Lys	Trp	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Tyr	Arg	DPro ^L Pro	1987.5
295.	SEQ ID NO:295	Tyr	Trp	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Tyr	Arg	DPro ^L Pro	2022.5
296.	SEQ ID NO:296	Trp	Trp	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Tyr	Arg	DPro ^L Pro	2045.5
297.	SEQ ID NO:297	Val	Trp	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Tyr	Arg	DPro ^L Pro	2082.4
298.	SEQ ID NO:298	Gln	Trp	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Tyr	Arg	DPro ^L Pro	1987.4
299.	SEQ ID NO:299	Cha	Trp	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Tyr	Arg	DPro ^L Pro	2012.5
300.	SEQ ID NO:300	Y(bzl)	Trp	Leu	Lys	Lys	Arg	Arg	Trp	Lys	Tyr	Tyr	Arg	DPro ^L Pro	2112.6

1.2. Procedure 2

Examples ex.256-275 were also synthesized using procedure 2.

The peptide synthesis was carried out by solid phase method using standard Fmoc chemistry on a peptide synthesizer-ABI 433A.

The first amino acid, Fmoc-Arg(Pbf)-OH (1.29g, 1.2 equiv.) was coupled to the 2-chlorotritylchloride resin (Barlos et al. *Tetrahedron Lett.* 1989, 30, 3943-3946) (2g, 0.83 mmol/g) in presence of DIEA (1.12mL, 4 equiv.) in CH₂Cl₂ (20 mL), with swirling for 3 hr at room temperature. The resin was then washed with 3 x CH₂Cl₂ /MeOH/DIEA(17:2:1), 3 x CH₂Cl₂, 2 x DMF, 2 x CH₂Cl₂, 2 x MeOH. Finally, the resin was dried under vacuum and the substitution level was measured by weight increase (~0.6 mmol/g)

The resin with the synthesized linear peptide, Fmoc-Arg(Pbf)-Trp(Boc)-Lys(Boc)-Tyr(tBu)-Arg(Pbf)-Val-^DPro-212-Leu-Arg(Pbf)-Leu-Lys(Boc)-Lys(Boc)-Arg(Pbf)-resin, was preferably divided into equal parts and placed in different reaction vessels in order to carry out the acylation reaction in parallel format. The coupling and deprotection reactions in the following steps were monitored by Kaiser's test (Kaiser et al. *Anal. Biochemistry* 1970, 43, 595).

Removal of Alloc protecting group:

To the linear peptide resin (100 mg in each reaction vessel) was added Pd(PPh₃)₄ (15mg, 0.5 equiv.) under argon followed by dry CH₂Cl₂ (10 mL) and phenylsilane (17μL, 30 equiv.). The reaction mixture was left for 1 hour in the dark, filtered, and the resin was washed twice with CH₂Cl₂, DMF, and CH₂Cl₂.

Acylation of 4-amino-proline group

To the resin was added the corresponding acylating agent (usually a carboxylic acid (R^{64'}COOH, 3 equiv.), HBTU (22.3mg, 4 equiv.), HOBT (8mg, 4 equiv.) and DIEA (125μL, 6 equiv.) in DMF (2mL) for 1.5-2 hrs at room temperature. The resin was filtered, washed with 2 x DMF, 3 x CH₂Cl₂, 2 x DMF.

Deprotection of N^α-Fmoc group:

Deprotection of the Fmoc-group was achieved by treating the resin with 20% piperidine in DMF for 20 min. The resin was subsequently filtered and washed three times with DMF, and CH₂Cl₂, and twice with DMF, and CH₂Cl₂.

Cleavage of peptide from the resin:

5 The linear side-chain protected peptide was cleaved from the resin using AcOH: TFE: CH₂Cl₂ (2:2:6, v/v/v) for 2 hrs at room temperature. The resin was filtered off and washed twice with a mixture of AcOH:TFE:DCM and once with CH₂Cl₂. The filtrate was subsequently diluted with hexane (14 times by vol.) and concentrated. Evaporation was repeated twice with hexane to remove traces of AcOH. The residue was dried under vacuum. Yield of the linear protected peptide was generally about 40-50 mg.

10

Cyclization of the linear protected peptide:

15 Cyclization was carried out in DMF at a concentration of 5 mg/mL using HATU (13.12 mg, 3 equiv.), HOAT (4.7 mg, 3 equiv.), DIEA (153 μL, 6 equiv.). The reaction mixture was stirred for 16 hrs at room temperature and the completion of reaction was monitored by HPLC. After the evaporation of DMF, CH₃CN/H₂O (90/10, v/v) was added to the residue and extracted with DCM. The organic layer was washed once with water and evaporated to dryness. Dried under vacuum.

20 *Cleavage of side chain protecting groups:*

The final deprotection of the side-chain protecting groups was carried out by treating the peptide with TFA:triisopropylsilane:H₂O (95:2.5:2.5, v/v/v) at room temperature for 3 hrs. TFA was then evaporated and the residue triturated with cold ether.

25

Purification:

30 The crude peptides thus obtained were analyzed and purified by HPLC on a VYDAC C18 preparative column using 5-60% CH₃CN/H₂O+0.1%TFA in 30 min as gradient and a flow rate of 10ml/min. The purity of the final peptide was checked by analytical HPLC and by ESI-MS. Analytical data are shown in table 7.

1.3. Procedure 3

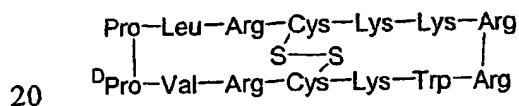
35 **Procedure 3** describes the synthesis of peptides having disulfide β-strand linkages.

- a) n=8: The peptides are synthesized according to **procedure 1** starting with the amino acid at position P4, coupled to the resin. The linear peptides are synthesized on solid support according to **procedure 1** in the following sequence: P5-P6-P7-P8-^DPro-Pro-P1-P2-P3-P4-resin, where at positions P2 and P7 Fmoc-Cys(Acm)OH or Fmoc-hCys(Acm)OH are incorporated. The linear peptides are cleaved and cyclized as described in **procedure 1**. The cyclized side chain protected β -hairpin mimetics are dissolved in methanol (0.5ml) to which is added dropwise a solution of iodine in methanol (1N, 1.5equiv.) at room temperature. The reaction mixture is stirred for 4 hours at room temperature and the solvent evaporated. The crude product is subsequently deprotected and purified as described in **procedure 1**.
- b) n=9: The peptides are synthesized according to **procedure 1** starting with the amino acid at position P5, coupled to the resin. The linear peptides are synthesized on solid support according to **procedure 1** in the following sequence: P6-P7-P8-P9-^DPro-Pro-P1-P2-P3-P4-P5-resin, where at positions P2 and P8 Fmoc-Cys(Acm)OH or Fmoc-hCys(Acm)OH are incorporated. The linear peptides are cleaved and cyclized as described in **procedure 1**. The cyclized side chain protected β -hairpin mimetics are dissolved in methanol (0.5ml) to which is added dropwise a solution of iodine in methanol (1N, 1.5equiv.) at room temperature. The reaction mixture is stirred for 4 hours at room temperature and the solvent evaporated. The crude product is subsequently deprotected and purified as described in **procedure 1**.
- c) n=10: The peptides are synthesized according to **procedure 1** starting with the amino acid at position P5, coupled to the resin. The linear peptides are synthesized on solid support according to **procedure 1** in the following sequence: P6-P7-P8-P9-P10-^DPro-Pro-P1-P2-P3-P4-P5-resin, where at positions P3 and P8 Fmoc-Cys(Acm)OH or Fmoc-hCys(Acm)OH are incorporated. The linear peptides are cleaved and cyclized as described in **procedure 1**. The cyclized side chain protected β -hairpin mimetics are dissolved in methanol (0.5ml) to which is added dropwise a solution of iodine in methanol (1N, 1.5equiv.) at room temperature. The reaction mixture is stirred for 4 hours at room temperature and the solvent evaporated. The crude product is subsequently deprotected and purified as described in **procedure 1**.
- d) n=11: The peptides are synthesized according to **procedure 1** starting with the amino acid at position P5, coupled to the resin. The linear peptides are synthesized on solid support according to **procedure 1** in the following sequence: P6-P7-P8-P9-P10-P11-^DPro-Pro-P1-P2-P3-P4-P5-resin, or P6-P7-P8-P9-P10-P11-^DPro-Pro-P1-P2-P3-P4, or P5-P6-P7-P8-P9-P10-P11-^DPro-Pro-P1-P2-P3-P4-P5-resin, where at positions P2, P4, P8 and P10 Fmoc-Cys(Acm)OH or Fmoc-hCys(Acm)OH are incorporated. The linear peptides are cleaved and

cyclized as described in **procedure 1**. The cyclized side chain protected β -hairpin mimetics are dissolved in methanol (0.5ml) to which is added dropwise a solution of iodine in methanol (1N, 1.5equiv.) at room temperature. The reaction mixture is stirred for 4 hours at room temperature and the solvent evaporated. The crude product is subsequently deprotected and purified as described in **procedure 1**.

e) $n=12$: The peptides are synthesized according to **procedure 1** starting with the amino acid at position P6, coupled to the resin. The linear peptides are synthesized on solid support according to **procedure 1** in the following sequence: P7-P8-P9-P10-P11-P12-^DPro-Pro-P1-P2-P3-P4-P5-P6-resin, or P7-P8-P9-P10-P11-^DPro-Pro-P1-P2-P3-P4-P5-P6-resin, or P7-P8-P9-P10-P11-^DPro-Pro-P1-P2-P3-P4-P5-P6-resin, where at positions P2, P4, P9 and P11 Fmoc-Cys(Acm)OH or Fmoc-hCys(Acm)OH are incorporated. The linear peptides are cleaved and cyclized as described in **procedure 1**. The cyclized side chain protected β -hairpin mimetics are dissolved in methanol (0.5ml) to which is added dropwise a solution of iodine in methanol (1N, 1.5equiv.) at room temperature. The reaction mixture is stirred for 4 hours at room temperature and the solvent evaporated. The crude product is subsequently deprotected and purified as described in **procedure 1**.

Ex.301:



Following **procedure 3** $\text{NH}_2\text{Arg(Pbf)}\text{-Lys(Boc)-Lys(Boc)-Cys(Acm)-Arg(Pbf)-Leu-Pro-}^D\text{Pro-Val-Arg-Cys(Acm)-Lys(Boc)-Trp(Boc)-Arg(Pbf)-}$ [SEQ ID NO:301], coupled to the resin, was synthesized on the resin, the linear side-chain protected peptide cleaved and cyclized, followed by disulfide formation, deprotection and preparative HPLC chromatography yielding the above product [SEQ ID NO:302] as a white amorphous powder. ESI-MS: 1806.2 ([M+H]⁺).

f) $n=14$: The peptides are synthesized according to **procedure 1** starting with the amino acid at position P7, coupled to the resin. The linear peptides are synthesized on solid support according to **procedure 1** in the following sequence: P8-P9-P10-P11-P12-P13-P14-^DPro-Pro-P1-P2-P3-P4-P5-P6-P7-resin, or P8-P9-P10-P11-P12-P13-P14-^DPro-Pro-P1-P2-P3-P4-P5-P6-P7-resin, or P8-P9-P10-P11-P12-P14-^DPro-Pro-P1-P2-P3-P4-P5-P6-P7-resin, where at positions P3, P5, P10 and P12 Fmoc-Cys(Acm)OH or Fmoc-hCys(Acm)OH are incorporated. The linear peptides are cleaved and cyclized as described in **procedure 1**. The

cyclized side chain protected β -hairpin mimetics are dissolved in methanol (0.5ml) to which is added dropwise a solution of iodine in methanol (1N, 1.5equiv.) at room temperature. The reaction mixture is stirred for 4 hours at room temperature and the solvent evaporated. The crude product is subsequently deprotected and purified as described in **procedure 1**.

5

g) **n=16**: The peptides are synthesized according to **procedure 1** starting with the amino acid at position P8, coupled to the resin. The linear peptides are synthesized on solid support according to **procedure 1** in the following sequence: P9-P10-P11-P12-P13-P14-P15-P16-^DPro-Pro-P1-P2-P3-P4-P5-P6-P7-P8-resin, or P9-P10-P11-P12-P13-P14-P15-P16-^DPro-Pro-P1-P2-P3-P4-P5-P6-P7-P8-resin, or P9-P10-P11-P12-P13-P14-P15-P16-^DPro-Pro-P1-P2-P3-P4-P5-P6-P7-P8-resin, or P9-P10-P11-P12-P13-P14-P15-P16-^DPro-Pro-P1-P2-P3-P4-P5-P6-P7-P8-resin, or P9-P10-P11-P12-P13-P14-P15-P16-^DPro-Pro-P1-P2-P3-P4-P5-P6-P7-P8-resin, or P9-P10-P11-P12-P13-P14-P15-P16-^DPro-Pro-P1-P2-P3-P4-P5-P6-P7-P8-resin, or P9-P10-P11-P12-P13-P14-P15-P16-^DPro-Pro-P1-P2-P3-P4-P5-P6-P7-P8-resin, where at positions P2, P4, P6, P11, P13 and P15 Fmoc-Cys(Acm)OH or Fmoc-hCys(Acm)OH are incorporated. The linear peptides are cleaved and cyclized as described in **procedure 1**. The cyclized side chain protected β -hairpin mimetics are dissolved in methanol (0.5ml) to which is added dropwise a solution of iodine in methanol (1N, 1.5equiv.) at room temperature. The reaction mixture is stirred for 4 hours at room temperature and the solvent evaporated. The crude product is subsequently deprotected and purified as described in **procedure 1**.

20

1.4. Procedure 4

Procedure 4 describes the synthesis of peptides having amide β -strand linkages.

25

a) **n=8**: The peptides are synthesized according to **procedure 1** starting with the amino acid at position P4, coupled to the resin. The linear peptides are synthesized on solid support according to **procedure 1** in the following sequence: P5-P6-P7-P8-^DPro-Pro-P1-P2-P3-P4-resin, where at position P2 Fmoc-Asp(OAllyl)OH or Fmoc-Glu(OAllyl)OH, and at position P7 Fmoc-Orn(Alloc)OH or Fmoc-Lys(Alloc)OH are incorporated. Alternatively, at position P2 Fmoc-Orn(Alloc)OH or Fmoc-Lys(Alloc)OH, and at position P7 Fmoc-Asp(OAllyl)OH or Fmoc-Glu(OAllyl)OH are incorporated. The linear peptides are cleaved and cyclized, and the allyl groups are removed as described in **procedure 2**. The amide linkage is subsequently performed as described for the cyclization according to **procedures 1 and 2**, the side chain protective groups are removed and the products are purified as described in **procedures 1 and 2**.

35

2.

b) $n=9$: The peptides are synthesized according to **procedure 1** starting with the amino acid at position P5, coupled to the resin. The linear peptides are synthesized on solid support according to **procedure 1** in the following sequence: P6-P7-P8-P9-^DPro-Pro-P1-P2-P3-P4-P5-resin, where at position P2 Fmoc-Asp(OAllyl)OH or Fmoc-Glu(OAllyl)OH, and at position P8 Fmoc-Orn(Alloc)OH or Fmoc-Lys(Alloc)OH are incorporated. Alternatively, at position P2 Fmoc-Orn(Alloc)OH or Fmoc-Lys(Alloc)OH, and at position P8 Fmoc-Asp(OAllyl)OH or Fmoc-Glu(OAllyl)OH are incorporated. The linear peptides are cleaved and cyclized, and the allyl groups are removed as described in **procedure 2**. The amide linkage is subsequently performed as described for the cyclization according to **procedures 1** and **2**, the side chain protective groups are removed and the products are purified as described in **procedures 1** and **2**.

c) $n=10$: The peptides are synthesized according to **procedure 1** starting with the amino acid at position P5, coupled to the resin. The linear peptides are synthesized on solid support according to **procedure 1** in the following sequence: P6-P7-P8-P9-P10-^DPro-Pro-P1-P2-P3-P4-P5-resin, where at position P3 Fmoc-Asp(OAllyl)OH or Fmoc-Glu(OAllyl)OH, and at position P8 Fmoc-Orn(Alloc)OH or Fmoc-Lys(Alloc)OH are incorporated. Alternatively, at position P3 Fmoc-Orn(Alloc)OH or Fmoc-Lys(Alloc)OH, and at position P8 Fmoc-Asp(OAllyl)OH or Fmoc-Glu(OAllyl)OH are incorporated. The linear peptides are cleaved and cyclized, and the allyl groups are removed as described in **procedure 2**. The amide linkage is subsequently performed as described for the cyclization according to **procedures 1** and **2**, the side chain protective groups are removed and the products are purified as described in **procedures 1** and **2**.

d) $n=11$: The peptides are synthesized according to **procedure 1** starting with the amino acid at position P5, coupled to the resin. The linear peptides are synthesized on solid support according to **procedure 1** in the following sequence: P6-P7-P8-P9-P10-P11-^DPro-Pro-P1-P2-P3-P4-P5-resin, or P6-P7-P8-P9-P10-P11-^DPro-Pro-P1-P2-P3-P4-P5-resin, or P6-P7-P8-P9-P10-P11-^DPro-Pro-P1-P2-P3-P4-P5-resin; where at positions P2 and/or P4 Fmoc-Asp(OAllyl)OH or Fmoc-Glu(OAllyl)OH, and at positions P8 and/or P10 Fmoc-Orn(Alloc)OH or Fmoc-Lys(Alloc)OH are incorporated. Alternatively, at positions P2 and/or P4 Fmoc-Orn(Alloc)OH or Fmoc-Lys(Alloc)OH, and at positions P8 and/or P10 Fmoc-Asp(OAllyl)OH or Fmoc-Glu(OAllyl)OH are incorporated. The linear peptides are cleaved and cyclized, and the allyl groups are removed as described in **procedure 2**. The amide linkage is subsequently performed as described for the cyclization according to **procedures 1**

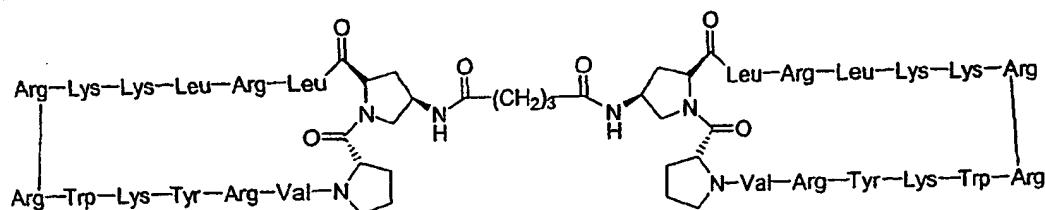
and 2, the side chain protective groups are removed and the products are purified as described in procedures 1 and 2.

e) $n=12$: The peptides are synthesized according to procedure 1 starting with the amino acid at position P6, coupled to the resin. The linear peptides are synthesized on solid support according to procedure 1 in the following sequence: P7-P8-P9-P10-P11-P12-^DPro-Pro-P1-P2-P3-P4-P5-P6-resin, or P7-P8-P9-P10-P11-P12-^DPro-Pro-P1-P2-P3-P4-P5-P6-resin, or P7-P8-P9-P10-P11-P12-^DPro-Pro-P1-P2-P3-P4-P5-P6-resin; where at positions P2 and/or P4 Fmoc-Asp(OAllyl)OH or Fmoc-Glu(OAllyl)OH, and at positions P9 and/or P11 Fmoc-Orn(Alloc)OH or Fmoc-Lys(Alloc)OH are incorporated. Alternatively, at positions P2 and/or P4 Fmoc-Orn(Alloc)OH or Fmoc-Lys(Alloc)OH, and at positions P9 and/or P11 Fmoc-Asp(OAllyl)OH or Fmoc-Glu(OAllyl)OH are incorporated. The linear peptides are cleaved and cyclized, and the allyl groups are removed as described in procedure 2. The amide linkage is subsequently performed as described for the cyclization according to procedures 1 and 2, the side chain protective groups are removed and the products are purified as described in procedures 1 and 2.

f) $n=14$: The peptides are synthesized according to procedure 1 starting with the amino acid at position P7, coupled to the resin. The linear peptides are synthesized on solid support according to procedure 1 in the following sequence: P8-P9-P10-P11-P12-P3-P14-^DPro-Pro-P1-P2-P3-P4-P5-P6-P7-resin, or P8-P9-P10-P11-P12-P13-P14-^DPro-Pro-P1-P2-P3-P4-P5-P6-P7-resin, or P8-P9-P10-P11-P12-R14-^DPro-Pro-P1-P2-P3-P4-P5-P6-P7-resin; where at positions P3 and/or P5 Fmoc-Asp(OAllyl)OH or Fmoc-Glu(OAllyl)OH, and at positions P10 and/or P12 Fmoc-Orn(Alloc)OH or Fmoc-Lys(Alloc)OH are incorporated. Alternatively, at positions P3 and/or P5 Fmoc-Orn(Alloc)OH or Fmoc-Lys(Alloc)OH, and at positions P10 and/or P12 Fmoc-Asp(OAllyl)OH or Fmoc-Glu(OAllyl)OH are incorporated. The linear peptides are cleaved and cyclized, and the allyl groups are removed as described in procedure 2. The amide linkage was subsequently performed as described for the cyclization according to procedures 1 and 2, the side chain protective groups are removed and the products are purified as described in procedures 1 and 2.

g) $n=16$: The peptides are synthesized according to procedure 1 starting with the amino acid at position P7, coupled to the resin. The linear peptides are synthesized on solid support according to procedure 1 in the following sequence: P8-P9-P10-P11-P12-P13-P14-P15-P16-^DPro-Pro-P1-P2-P3-P4-P5-P6-P7-resin, or P8-P9-P10-P11-P12-P13-P14-P15-P16-^DPro-Pro-P1-P2-P3-P4-P5-P6-P7-resin, or P9-P9-P10-P11-P12-P4-P5-P16-^DPro-Pro-P1-P2-P3-P4-P5-P6-P7-resin, or P8-P9-P10-P11-P12-P13-P14-P15-P16-^DPro-Pro-P1-P2-P3-P4-P5-P6-P7-

resin, or P8-P9-P10-P11-P12-P13-P14-P15-P16-DPro-Pro-P1-P2-P3-P4-P5-P6-P7-resin, or P8-P9-P10-P11-P12-P13-P14-P15-P16-DPro-Pro-P1-P2-P3-P4-P5-P6-P7-resin, or P8-P9-P10-P11-P12-P13-P14-P15-P16-DPro-Pro-P1-P2-P3-P4-P5-P6-P7-resin; where at positions P2 and/or P4 and/or P6 Fmoc-Asp(Oallyl)OH or Fmoc-Glu(Oallyl)OH, and at positions P11 and/or P13 and/or P15 Fmoc-Orn(Alloc)OH or Fmoc-Lys(Alloc)OH are incorporated. Alternatively, at positions P2 and/or P4 and/or P6 Fmoc-Orn(Alloc)OH or Fmoc-Lys(Alloc)OH, and at positions P11 and/or P13 and/or P15 Fmoc-Asp(Oallyl)OH or Fmoc-Glu(Oallyl)OH are incorporated. The linear peptides are cleaved and cyclized, and the allyl groups are removed as described in procedure 2. The amide linkage is subsequently performed as described for the cyclization according to procedures 1 and 2, the side chain protective groups are removed and the products are purified as described in procedures 1 and 2.

Ex.302:

15

Following procedure 2 NH₂Arg(Pbf)-Trp(Boc)-Lys(Boc)-Tyr(tBu)-Arg(Pbf)-DPro-212-Leu-Arg(Pbf)-Leu-Lys(Boc)-Lys(Boc)-Arg(Pbf)- [SEQ ID NO:303], coupled to the resin, was prepared, the linear peptide cleaved and cyclized. The Alloc-group was removed from building block 212 as described in procedure 2, half of the resulting amine reacted with excess glutaric anhydride in pyridine and DMAP and the solvents were removed. The resulting acid was coupled with the second half of the above mentioned amine in DMF and in the presence of TATU, HOAt and DIEA. The protective groups were removed as described in procedure 2 and the product purified by preparative HPLC chromatography as described in procedure 2 to yield the above product [SEQ ID NO:304] as a white amorphous powder. ESI-MS: 3882.3 ([M+H]⁺).

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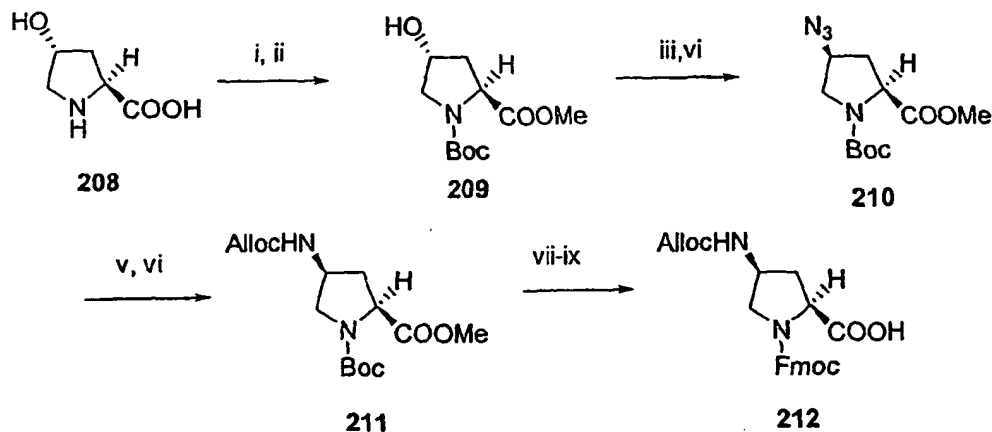
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2. Synthesis of templates

2.1. The synthesis of (2*S*,4*S*)-4-[(Allyloxy)carbonylamino]-1-[(9*H*-fluoren-9-yl)methoxycarbonyl]-proline (212) and (2*S*,4*R*)-4-[(Allyloxy)carbonylamino]-1-[(9*H*-fluoren-9-yl)methoxy-carbonyl]proline (217) are shown in Schemes 42 and 43.

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Scheme 42



i: SOCl_2 , MeOH; ii: Boc_2O , DMAP, Et_3N ; iii: $\text{pNO}_2\text{C}_6\text{H}_4\text{SO}_2\text{Cl}$, Et_3N ; iv: NaN_3 , DMF;
 v: SnCl_2 , dioxane/ H_2O ; vi: $\text{ClCOOCH}_2\text{CH}=\text{CH}_2$, aq. NaHCO_3 , dioxane; vii: LiOH , MeOH, H_2O ;
 viii: TFA, CH_2Cl_2 ; ix: Fmoc-OSu, DIEA

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(2*S*,4*S*)-4-[(Allyloxy)carbonylamino]-1-[(9*H*-fluoren-9-yl)methoxycarbonyl]-proline
 (212)

- i,ii:* To a solution of (2*S*,4*R*)-4-hydroxyproline (30 g, 0.18 mol) in abs. methanol (300 ml) at 0 °C thionyl chloride (38 ml, 2.5 eq, 0.45 mol) was added dropwise. The solution was heated to reflux and stirred for 3 h under nitrogen. Then the solution was concentrated by rotary evaporation and the ester precipitated by adding diethylether. After filtration the white solid was washed with diethylether, then dried at HV: (2*S*,4*R*)-4-hydroxyproline-methylester-hydrochloride as a white solid (29.9 g, 90 %). TLC ($\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{water}$ 70:28:2): R_f 0.82. $[\alpha]_D^{20} = -24.5$ ($c = 1.01$, MeOH). IR (KBr): 3378s (br.), 2950m, 2863w, 1745s, 1700s, 1590m, 1450s, 1415s, 1360s, 1215s, 1185s, 1080m, 700m. $^1\text{H-NMR}$ (300MHz, MeOH- d_4) 4.66-4.55 (m, 2H, H-C(4), H-C(2)); 3.85 (s, 3H, $\text{H}_3\text{C-O}$); 3.45 (dd, $J = 12.2, 3.8$, 1H, H-C(5)); 3.37-3.25 (m, 1H, H-C(5)); 2.44-2.34 (m, 1H, H-C(3)), 2.27-2.12 (m, 1H, H-C(3)). $^{13}\text{C-NMR}$ (75MHz, MeOH- d_4): 170.8 (s, COOMe); 70.8 (d, C(4)); 59.6 (d, C(2)); 55.2 (t, C(5)); 54.2 (q, Me); 38.7 (t, C(3)). CI-MS (NH_3): 146.1 ($[\text{M-Cl}]^+$).
- 30 g (0.17 mmol) of the above intermediate was dissolved in CH_2Cl_2 (300 ml), cooled to 0 °C and triethylamine (45 ml, 1.5 eq, 0.25 mol) was added dropwise. Then di-tert.-butyldicarbonate (54.0 g, 1.5 eq, 0.25 mmol) in CH_2Cl_2 (15 ml) and 4-*N,N*-dimethylaminopyridine (2.50 g, 0.1 eq, 17 mmol) was added and the solution stirred at room temperature overnight. Then the solution was washed with 1N aq. citric acid solution, sat. aq.

NaHCO₃ solution, dried (Na₂SO₄), evaporated and the residue dried at high vacuum: (2*S*,4*R*)-4-Hydroxy-1-[(*tert*-butoxy)carbonyl]proline-methylester (**209**) as a white solid (39.6 g, 78 %). TLC (CH₂Cl₂/MeOH 9:1): R_f 0.55. $[\alpha]_D^{24} = -55.9$ (c = 0.983, CHCl₃). IR (KBr): 3615w, 3440w (br.), 2980m, 2950m, 2880m, 1750s, 1705s, 1680s, 1480m, 1410s, 1370s, 1340m, 1200s, 1160s, 1130m, 1090m, 1055w, 960w, 915w, 895w, 855m, 715m. ¹H-NMR (300MHz, CDCl₃): 4.47-4.37 (m, 2H, H-C(4), H-C(2)); 3.73 (s, 3H, H₃C-O); 3.62 (dd, J = 11.8, 4.1, 1H, H-C(5)); 3.54-3.44 (m, 1H, H-C(5)); 2.32-2.25 (m, 1H, H-C(3)); 2.10-2.03 (m, 1H, H-C(3)); 1.46+1.41 (2s, 9H, *t*Bu). ¹³C-NMR (75 MHz, CDCl₃): 173.6 (s, COOMe); 154.3+153.9 (2s, COO*t*Bu); 80.3 (s, C-*t*Bu); 70.0+69.3 (2d, C(4)); 57.9+57.4 (2d, C(2)); 54.6 (t, C(5)); 51.9 (q, Me); 39.0+38.4 (2t, C(3)); 28.1+27.6 (2q, *t*Bu). CI-MS: 246.2 ([M+H]⁺); 190.1 ([M-*t*Bu+H]⁺); 146.1 ([M-BOC+H]⁺).

iii,iv: 39 g (0.16 mol) of **209** was dissolved in CH₂Cl₂ (300 ml) followed by addition of 4-nitrobenzenesulfonyl chloride (46 g, 1.3 eq, 0.21 mol) and Et₃N (33 ml, 1.5 eq, 0.24 mol) at 0 °C. Then the solution was stirred overnight and brought gradually to room temperature, washed with 1N hydrochloric acid, sat. aq. NaHCO₃ solution and dried (Na₂SO₄). The solvents were evaporated and the crude product was purified by filtration on silica gel with (2:1) hexane/AcOEt. The product was crystallized from hexane/AcOEt: (2*S*,4*S*)-4-[(*p*-nitrobenzyl)sulfonyloxy]-1-[(*tert*-butoxy)carbonyl]proline methylester as white crystals (46.4 g, 65 %). TLC (hexane/AcOEt 1:1): R_f 0.78. M.p.: 93-95 °C. $[\alpha]_D^{20} = -32.3$ ° (c = 0.907, CHCl₃). IR (KBr): 3110w, 3071w, 2971w, 1745s, 1696s, 1609s, 1532s, 1414s, 1365s, 1348m, 1289m, 1190m, 1173m, 1122w, 1097w, 1043w, 954w, 912w, 755w, 578w. ¹H-NMR (600MHz, CDCl₃): 8.42-8.34 (m, 2H, H-C(Nos)); 8.11-8.04 (m, 2H, H-C(Nos)); 5.14 (s, 1H, H-C(4)); 4.39-4.28 (m, 1H, H-C(2)); 3.70-3.56 (m, 5H, H₂-C(5), H₃C-O); 2.58-2.38 (m, 1H, H-C(3)); 2.25-2.11 (m, 1H, H-C(3)); 1.37+1.33 (2s, 9H, *t*Bu). ¹³C-NMR (150 MHz, CDCl₃): 172.4+172.2 (2s, COOMe); 153.6+153.0 (2s, COO*t*Bu); 150.8+142.0 (2s, C(Nos)); 129.0+124.6 (2d, C(Nos)); 80.4 (s, C-*t*Bu); 80.8+79.9 (2d, C(4)); 57.1+56.9 (2d, C(2)); 52.2+51.7 (2t, C(5)); 52.3 (q, Me); 37.1+35.9 (2t, C(3)); 28.0 (q, *t*Bu). ESI-MS (MeOH + NaI): 453.0 ([M+Na]⁺).

38 g (88 mmol) of the above intermediate was dissolved in DMF (450 ml) then heated to 40 °C when sodium azide (34 g, 6 eq, 0.53 mol) was added and the solution stirred overnight. DMF was evaporated and the solid suspended in diethylether. The suspension was washed with water and dried (Na₂SO₄). The solvent was evaporated and the product dried at high vacuum: (2*S*,4*S*)-4-Azido-1-[(*tert*-butoxy)carbonyl]proline methylester (**210**) yellow oil (21.1 g, 88 %). $[\alpha]_D^{20} = -36.9$ (c = 0.965, CHCl₃). ¹H-NMR (600MHz, CDCl₃): 4.46-4.25 (2m, 1H, H-C(2)); 4.20-4.10 (m, 1H, H-C(4)); 3.80-3.65 (m, 4H, H-C(5), H₃C-O); 3.53-3.41 (m, 1H, H-C(5)); 2.54-2.39 (m, 1H, H-C(3)); 2.21-2.12 (m, 1H, H-C(3)); 1.47+1.41 (2s, 9H, *t*Bu). ¹³C-

NMR (150 MHz, CDCl₃): 172.2+171.9 (2s, COOMe); 153.9+153.4 (2s, COOtBu); 80.5 (s, C-*t*Bu); 59.2+58.2 (2d, C(4)); 57.7+57.3 (2d, C(2)); 52.4+52.2 (2q, Me); 51.2+50.7 (2t, C(5)); 36.0+35.0 (2t, C(3)); 28.3+28.2 (2q, *t*Bu). EI-MS (70ev): 270.1 ([M]⁺); 227.1 ([M-CO₂+H]⁺); 169.1 ([M-BOC+H]⁺).

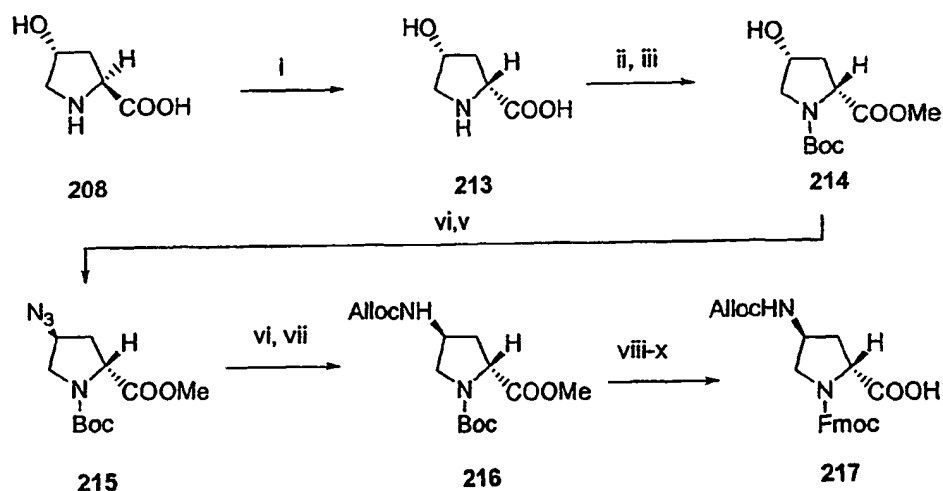
- 5 *v. vi.* 21.1 g (78 mmol) of the above intermediate was dissolved in a (3:1)-mixture of dioxane/water (500 ml) and SnCl₂ (59.2 g, 4 eq, 0.31 mol) was added at 0° and the solution stirred for 30 min. and gradually brought to room temperature and stirred for another 5h. After adjusting the pH to 8 with solid NaHCO₃, allyl chloroformate (41.5 ml, 5 eq, 0.39 mol) was added and the solution stirred at room temperature overnight. The reaction mixture was
- 10 evaporated and extracted with AcOEt. The organic phase was washed with brine, dried (Na₂SO₄), the solvent evaporated and the product was dried at high vacuum: (2*S*,4*S*)-4-[(Allyloxy)carbonylamino]-1-[(*tert*-butoxy)carbonyl]proline methylester (211) as a clear thick oil (22.3 g, 87 %). $[\alpha]_D^{20} = -30.2^\circ$ (c = 1.25, CHCl₃). ¹H-NMR (300MHz, CDCl₃): 5.98-5.77 (m, 1H, H-C(β)(Alloc)); 5.32-5.12 (m, 2H, H₂-C(γ)(Alloc)); 4.59-4.46 (m, 2H, H₂-
- 15 C(α)(Alloc)); 4.40-4.16 (m, 2H, H-C(4), H-C(2)); 3.80-3.53 (m, 4H, H-C(5), H₃C-O); 3.53-3.31 (m, 1H, H-C(5)); 2.54-2.17 (m, 1H, H-C(3)); 1.98-1.84 (m, 1H, H-C(3)); 1.41+1.37 (2s, 9H, *t*Bu). ESI-MS (MeOH+ CH₂Cl₂): 351.2 ([M+Na]⁺); 229.0 ([M-BOC+H]⁺).

- vii-ix*: 22 g, 67 mmol) of 211 was dissolved in a (4:1)-mixture of methanol/water (100 ml) and LiOH (5 g, 2 eq, 134 mmol) was added at room temperature and the solution stirred
- 20 for 3.5 h. The reaction mixture was evaporated and extracted with 1*N* hydrochloric acid (100 ml) and AcOEt. The solvent was removed and the resulting solid dissolved in 1:1 TFA/CH₂Cl₂ (200ml) and stirred for 2 h. The solvents were evaporated and the product dried at high vacuum: (2*S*,4*S*)-4-[(Allyloxy)carbonylamino]proline as a clear oil (21 g, 96 %) ¹H-NMR (600MHz, MeOH-d₄): 5.98-5.85 (m, 1H, H-C(β)(Alloc)); 5.30 (*dd*, J=17.1, 1.5 Hz, 1H, H-C(γ)(Alloc)); 5.12 (*d*, J=10.7 Hz, 1H, H-C(γ)(Alloc)); 4.54 (*d*, J=4.4 Hz, 2H, H₂-
- 25 C(α)(Alloc)); 4.44 (*t*, J=8.9 Hz, 1H, H-C(2)); 4.36-4.27 (m, 1H, H-C(4)); 3.58 (*dd*, J=12.2, 7.3 Hz, 1H, H-C(5)); 3.34-3.32 (m, 1H, H-C(5)); 2.73 (*ddd*, J=13.6, 8.7, 7.2 Hz, 1H, H-C(3)); 2.23-2.15 (m, 1H, H-C(3)). ¹³C-NMR (150 MHz, MeOH-d₄): 171.3 (s, COOMe); 158.3 (s, COOAllyl); 134.1 (*d*, C(β)(Alloc)); 118.0 (*t*, C(γ)(Alloc)); 66.8 (*t*, C(α)(Alloc)); 59.7 (*d*, C(2)); 51.3 (*d*, C(4)); 51.1 (*t*, C(5)); 34.9 (*t*, C(3)). ESI-MS (DCM+MeOH): 237.0 ([M+Na]⁺); 215.0 ([M+H]⁺).
- 30

- 15 g (70 mmol) of the above intermediate and 9-fluorenylmethoxycarbonylsuccinimid (28 g, 1.2 eq, 84 mmol) were dissolved in DCM (700 ml) and DIEA (48 ml, 6 eq, 0.42 mol) was added and the solution stirred overnight at room temperature. The solvent was removed and
- 35 the residue dissolved in AcOEt and washed with 1*N* hydrochloric acid and dried (Na₂SO₄). After evaporation, the crude product was purified by filtration on silica gel with a gradient of

(3:1) hexane/AcOEt to AcOEt. The solvent was evaporated and the residue crystallized from hexane at -20 °C. The product was dried at high vacuum: (2*S*,4*S*)-4-[(Allyloxy)carbonylamino]-1-[(9*H*-fluoren-9-yl)methoxycarbonyl]-proline (212) as a white solid (23.8 mg, 78 %) [α]_D²⁰ = -27.0 (*c* = 1.1, CHCl₃). IR (KBr): 3321*w* (br.), 3066*w*, 2953*w*, 1707*s*, 1530*m*, 1451*s*, 1422*s*, 1354*m*, 1250*m*, 1205*m*, 1173*m*, 1118*m*, 1033*m*, 977*m*, 936*m*, 759*m*, 739*s*, 621*m*, 597*w*, 571*w*, 545*s*. ¹H-NMR (300MHz, MeOH-*d*₄): 7.88-7.78 (*m*, 2H, H-C(4')(Fmoc)); 7.71-7.61 (*m*, 2H, H-C(1')(Fmoc)); 7.49-7.29 (*m*, 4H, H-C(3')(Fmoc), H-C(2')(Fmoc)); 6.08-5.68 (*m*, 1H, H-C(β)(Alloc)); 5.41-5.17 (*m*, 2H, H₂-C(γ)(Alloc); 4.58 (*s*, 2H, H₂-C(α)(Alloc)); 4.74-4.17 (*m*, 5H, H₂-C(10')(Fmoc), H-C(9')(Fmoc), H-C(4), H-C(2)); 3.94-3.73 (*m*, 1H, H-C(5)); 3.41-3.26 (*m*, 1H, H-C(5)); 2.74-2.54 (*m*, 1H, H-C(3)); 2.12-1.92 (*m*, 1H, H-C(3)). ESI-MS (DCM+MeOH): 459.3 ([*M*+Na]⁺); 437.3 ([*M*+H]⁺).

Scheme 43



i: Ac_2O , AcOH ; ii: SOCl_2 , MeOH ; iii: Boc_2O , DMAP , Et_3N ; vi: $\text{pNO}_2\text{C}_6\text{H}_4\text{SO}_2\text{Cl}$, Et_3N ; v: NaN_3 , DMF ; vi: SnCl_2 , dioxane/ H_2O ; vii: $\text{ClCOOCH}_2\text{CH}=\text{CH}_2$, aq. NaHCO_3 , dioxane; viii: LiOH , MeOH , H_2O ; ix: TFA , CH_2Cl_2 ; x: Fmoc-OSu , DIEA

5 2.2. (2*R*,4*S*)-4-[(Allyloxy)carbonylamino]-1-[(9*H*-fluoren-9-yl)methoxycarbonyl]-proline (217)

i: A solution of acetic anhydride (1.02 kg, 5.3eq, 10 mol) in glacial acetic acid (3 l) was heated to 50 °C and (2*S*,4*R*)-4-hydroxyproline (208) (247 g, 1.88 mol) was added in one
 10 portion. The solution was refluxed for 5.5 h., cooled to room temperature and the solvent was removed under reduced pressure giving a thick oil. The oil was then dissolved in 2*N* hydrochloric acid (3.5 l) and heated to reflux for 4 h and treated with charcoal and filtered through Celite. As the solution was evaporated, white needles formed, which were filtered. The product was dried at high vacuum: (2*R*,4*R*)-4-hydroxyproline-hydrochloride (213) white
 15 cryst. needles (220.9 g, 70 %). M.p.: 117 °C. $[\alpha]_D^{20} = +19.3^\circ$ ($c = 1.04$, water). IR (KBr): 3238s, 3017s, 2569m, 1712s, 1584m, 1376s, 1332m, 1255s, 1204m, 1181w, 1091w, 1066w, 994w, 725m, 499s. $^1\text{H-NMR}$ (600MHz, MeOH-d_4): 9.64 (s, 1H, H-N); 8.89 (s, 1H, H-N); 4.55-4.53 (m, 1H, H-C(4)); 4.51 (dd, $J = 10.4, 3.6$ Hz, 1H, H-C(2)); 3.44-3.35 (m, 2H, H₂-C(5)); 2.54-2.48 (m, 1H, H-C(3)); 2.40-2.34 (m, 1H, H-C(3)). $^{13}\text{C-NMR}$ (150MHz, MeOH-d_4): 171.9 (s, COOH); 70.3 (d, C(4)); 59.6 (d, C(2)); 55.0 (t, C(5)); 38.5 (t, C(3)). EI-MS
 20 (NH_3): 132.1 ($[\text{M}-\text{Cl}]^+$). The filtrate was further concentrated to give an additional 59.5 g (19 %).

ii,iii: To a solution of 213 (30 g, 0.18 mol) in abs. methanol (550 ml) was added dropwise at 0 °C thionyl chloride (38 ml, 2.5 eq, 0.45 mol). The solution refluxed for 3 h under nitrogen

atmosphere. The solution was evaporated and the ester hydrochloride precipitated by adding diethylether. After filtration the white solid was washed with diethylether and dried at high vacuum: (2*R*,4*R*)-4-hydroxyproline methylester-hydrochloride white solid (29 g, 89 %).

- [α]_D²⁰ = +8.6 ° (c = 0.873, MeOH). IR (KBr): 3388s (br.), 2980s (br.), 1730s, 1634m, 1586s, 1384s, 1248s, 1095s, 1064s, 1030m, 877m. ¹H-NMR (300MHz, MeOH-d₄): 4.59-4.44 (m, 2H, H-C(4), H-C(2)); 3.81 (s, 3H, H₃C-O); 3.37-3.31 (m, 2H, H₂-C(5)); 2.50-2.37 (m, 1H, H-C(3)), 2.37-2.27 (m, 1H, H-C(3)). ¹³C-NMR (75MHz, MeOH-d₄): 170.9 (s, COOMe); 70.2 (d, C(4)); 59.8 (d, C(2)); 55.1 (t, C(5)); 54.1 (q, C(Me)); 38.4 (t, C(3)). EI-MS (NH₃): 146.1 ([M-Cl]⁺).
- 10 10 g (55 mmol) of the above intermediate was dissolved in CH₂Cl₂ (100 ml), cooled to 0 °C and triethylamine (15.2 ml, 2 eq, 0.11 mol) was added dropwise. Then di-tert.-butyldicarbonate (18.0 g, 1.5 eq, 83 mmol) in CH₂Cl₂ (10 ml) and 4-*N,N*-dimethylaminopyridine (0.67 g, 0.1 eq, 5 mmol) were added and the solution was stirred at RT overnight. The solution was washed with 1M aq. citric acid solution and sat. aqueous
- 15 NaHCO₃ solution, dried (Na₂SO₄), the solvents evaporated and dried at high vacuum: (2*R*,4*R*)-4-hydroxy-1-[(*tert*-butoxy)-carbonyl]prolinemethylester (214) as a white solid (13 g, 97 %). [α]_D²⁰ = +13.0 ° (c = 1.06, CHCl₃). IR (KBr): 3466s (br.), 2985s, 2930m, 1729s, 1679s, 1424s, 1283m, 1262m, 1122s, 1089s, 969m, 770m. ¹H-NMR (300MHz, CDCl₃): 4.43-4.26 (m, 2H, H-C(4), H-C(2)); 3.80+3.79 (2s, 3H, H₃C-O); 3.76-3.47 (m, 2H, H₂-C(5)); 2.44-2.24 (m, 1H, H-C(3)); 2.16-2.03 (m, 1H, H-C(3)); 1.47+1.43 (2s, 9H, *t*Bu). ESI-MS: 268.1 ([M+Na]⁺).
- 20 *iv,v*: 214 (12.2 g, 50 mmol) was dissolved in CH₂Cl₂ (130 ml), cooled to 0 °C and 4-nitrobenzenesulfonyl chloride (14.3 g, 1.3 eq, 65 mmol) and Et₃N (10.3 ml, 1.5 eq, 75 mmol) were added. The reaction mixture was stirred overnight and gradually brought to room temperature. The solution was washed with 1N hydrochloric acid and saturated aqueous
- 25 NaHCO₃ solution, dried (Na₂SO₄), the solvents were evaporated and the crude product was purified by filtration on silica gel with (2:1)-mixture of hexane/AcOEt: 18 g (84 %). The product was then recrystallized from hexane/AcOEt: (2*R*,4*R*)-4-[(*p*-nitrobenzyl)sulfonyloxy]-1-[(*tert*-butoxy)carbonyl]proline-methylester as white crystals (13.7 g, 64 %). TLC (hexane/AcOEt 1:1): R_f 0.76. M.p.: 113-115 °C. [α]_D²⁰ = +21.6 ° (c = 0.924, CHCl₃). IR
- 30 (KBr): 3112s (br.), 2981s, 2955s, 2882m, 1755s, 1683s, 1532s, 1413s, 1375s, 1348s, 1192s, 928s, 911s, 759m, 745s, 610s. ¹H-NMR (600MHz, CDCl₃): 8.45-8.35 (m, 2H, H-C(Nos)); 8.15-8.06 (m, 2H, H-C(Nos)); 5.27-5.16 (m, 1H, H-C(4)); 4.53-4.32 (m, 1H, H-C(2)); 3.75-3.60 (m, 5H, H₂-C(5), H₃C-O); 2.59-2.35 (m, 2H, H₂-C(3)); 1.42+1.39 (2s, 9H, *t*Bu). ¹³C-NMR (150 MHz, CDCl₃): 171.8 + 171.6 (s, COOMe); 153.8+153.4 (s, COO*t*Bu);
- 35 151.0+142.6 (s, C(Nos)); 129.2+124.7 (d, C(Nos)); 81.0 (s, C-*t*Bu); 80.8+79.7 (d, C(4));

57.4+57.1 (*d*, C(2)); 52.6+52.5+52.3+51.8 (*t*, C(5), *q*, Me); 37.2+36.3 (*t*, C(3)); 28.5+28.3 (*q*, *t*Bu). ESI-MS (DCM + MeOH + NaI): 453.2 ($[M+Na]^+$).

13 g (30 mmol) of the above intermediate was dissolved in DMF (200 ml), heated to 40 °C and sodium azide (14.3 g, 6 eq, 180 mmol) was added and the reaction mixture stirred overnight. The reaction mixture was evaporated and the residue suspended in diethylether. The suspension was filtered, the filtrate washed with water and the organic phase dried (Na_2SO_4). The solvent was evaporated and the product dried at high vacuum: (2*R*,4*S*)-4-azido-1-[(*tert*-butoxy)carbonyl]prolinemethylester (215) as a yellow oil (8.15 g, 99 %). $[\alpha]_D^{20} = +42.8^\circ$ (*c* = 1.05, $CHCl_3$). 1H -NMR (300MHz, $CDCl_3$): 4.58-4.37 (*m*, 1H, H-C(2)); 4.34-4.23 (*m*, 1H, H-C(4)); 3.92-3.51 (*m*, 5H, H_2 -C(5), H_3 C-O); 2.52-2.33 (*m*, 1H, H-C(3)); 2.33-2.20 (*m*, 1H, H-C(3)); 1.56+1.51 (2*s*, 9H, *t*Bu). CI-MS (NH_3): 288.2 ($[M+NH_4]^+$); 271.1 ($[M+H]^+$).

vi, vii: 215 (8 g, 30 mmol) was dissolved in a (3:1)-mixture of dioxane/water (400 ml), cooled to 0 °C and $SnCl_2$ (22.4 g, 4 eq, 120 mmol) was added and the reaction mixture stirred for 30 min. at 0°, gradually warmed to room temperature and stirred for another 5h. After adjusting the pH of the solution to 8 with solid $NaHCO_3$, allyl chloroformate (15.7 ml, 5 eq, 150 mmol) was added. The reaction mixture was stirred overnight at room temperature, evaporated and extracted with AcOEt and the organic phase washed with brine. After drying the organic phase (Na_2SO_4), the solvent was evaporated and the product dried at high vacuum: (2*R*,4*S*)-4-[(Allyloxy)carbonylamino]-1-[(*tert*-butoxy)carbonyl] proline-methylester as a clear thick oil (216) (8.7 g, 89 %). $[\alpha]_D^{20} = +41.9^\circ$ (*c* = 0.928, $CHCl_3$). 1H -NMR (300MHz, $CDCl_3$): 5.98-5.87 (*m*, 1H, H-C(β)(Alloc)); 5.34-5.02 (*m*, 2H, H_2 -C(γ)(Alloc)); 4.62-4.49 (*m*, 2H, H_2 -C(α)(Alloc)); 4.41-4.23 (*m*, 2H, H-C(4), H-C(2)); 3.82-3.66 (*m*, 4H, H-C(5), H_3 C-O); 3.43-3.20 (*m*, 1H, H-C(5)); 2.33-2.07 (*m*, 2H, H_2 -C(3)); 1.43+1.39 (2*s*, 9H, *t*Bu). CI-MS (NH_3): 329.1 ($[M+H]^+$).

vii-x: 216 (8.4 g, 25 mmol) was dissolved in (4:1)-mixture of methanol/water (100 ml) at room temperature, LiOH (2.2 g, 2 eq, 50 mmol) added and the solution stirred overnight. Methanol was evaporated and the residue poured onto 1*N* hydrochloric acid (100 ml) and extracted with AcOEt. The solvent was removed and the residue dissolved in (1:1)-mixture of TFA/ CH_2Cl_2 (200ml) and stirred for 2h. The solvents were evaporated and the product dried at high vacuum: (2*R*,4*R*)-4-[(Allyloxy)carbonylamino]proline as a clear oil (5.2 g, 96 %) 1H -NMR (300MHz, $MeOH-d_4$): 6.04-5.88 (*m*, 1H, H_2 -C(β)(Alloc)); 5.38-5.19 (*m*, 2H, H_2 -C(γ)(Alloc)); 4.64-4.54 (*m*, 3H, H_2 -C(α)(Alloc), H-C(4)); 4.39-4.22 (*m*, 1H, H-C(2)); 3.71-3.60 (*m*, 1H, H-C(5)); 3.45-3.32 (*m*, 1H, H-C(5)); 2.51-2.41 (*m*, 2H, H_2 -C(3)). CI-MS (NH_3): 215.1 ($[M+H]^+$).

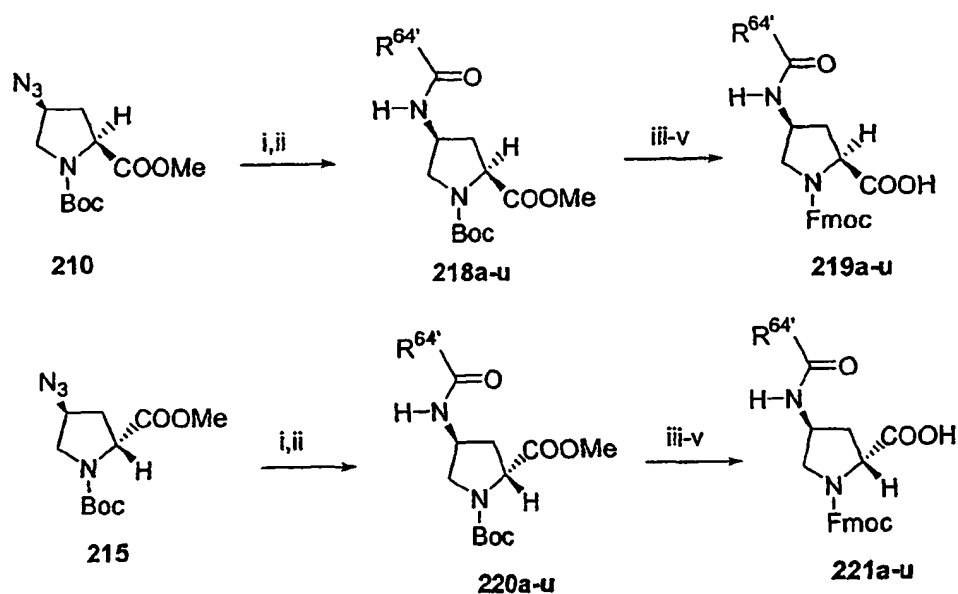
200 mg (0.86 mmol) of the above intermediate and 9-fluorenylmethoxycarbonylsuccinimide (440 mg, 1.5 eq, 1.3 mmol) were dissolved in CH_2Cl_2 (10 ml) and DIEA (466 μl, 4 eq, 3.44

mmol) was added, and the solution stirred overnight at room temperature. The solvent was removed and the residue dissolved in AcOEt, washed with 1*N* hydrochloric acid dried (Na₂SO₄). After evaporation, the crude product was purified by filtration over silica gel with first a gradient of (3:1) hexane/AcOEt to AcOEt. The solvent was coevaporated with CH₂Cl₂ and the product dried at high vacuum: (2*R*,4*S*)-4-[(Allyloxy)carbonylamino]-1-[(9*H*-fluoren-9-yl)methoxy-carbonyl]- proline (217) white solid (90 mg, 33 %) [α]_D²⁰ = +29.3 ° (c = 1.08, CHCl₃). IR (KBr): 3314s (br.), 3066s (br.), 2952s (br.), 1708s (br.), 1536m, 1424s, 1353s, 1126m, 1030m, 909m, 759m, 738s, 620m. ¹H-NMR (300MHz, CDCl₃): 8.74 (s, 1H, H-N); 7.79-7.66 (m, 2H, H-C(4')(fmoc)); 7.62-7.49 (m, 2H, H-C(1')(fmoc)); 7.44-7.22 (m, 4H, H-C(3')(fmoc), H-C(2')(fmoc)); 6.03-5.74 (m, 1H, H-C(β)(Alloc)); 5.41-5.07 (m, 2H, H₂-C(γ)(Alloc); 4.74-4.17 (m, 7H, H₂-C(10')(fmoc), H-C(9')(fmoc), H-C(4), H-C(2), H₂-C(α)(Alloc)); 3.91-3.76 (m, 1H, H-C(5)); 3.48-3.25 (m, 1H, H-C(5)); 2.45-2.08 (m, 2H, H₂-C(3)). ESI-MS (MeOH): 437.3 ([M+H]⁺); ESI-MS (MeOH+Na): 459.1 ([M+Na]⁺).

2.3. Starting from derivatives 210 and 215 the key precursors 219a-u and 221a-u can be prepared according to *Scheme 44*.

R⁶⁴: n-hexyl (219a, 221a); n-heptyl (219b, 221b); 4-(phenyl)benzyl (219c, 221c); diphenylmethyl (219d, 221d); 3-amino-propyl (219e, 221e); 5-amino-pentyl (219f, 221f); methyl (219g, 221g); ethyl (219h, 221h); isopropyl (219i, 221i); isobutyl (219k, 221k); n-propyl (219l, 221l); cyclohexyl (219m, 221m); cyclohexylmethyl (219n, 221n); n-butyl (219o, 221o); phenyl (219p, 221p); benzyl (219q, 221q); (3-indolyl)methyl (219r, 221r); 2-(3-indolyl)ethyl (219s, 221s); (4-phenyl)phenyl (219t, 221t); n-nonyl (219u, 221u).

Scheme 44



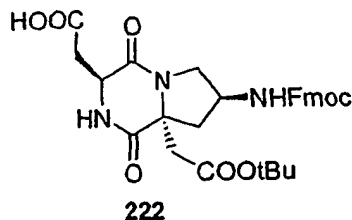
i: SnCl₂, dioxane/H₂O; ii: R^{64'}COCl, diisopropylethylamine, CH₂Cl₂; iii: LiOH·H₂O, MeOH, H₂O; iv: TFA, CH₂Cl₂; v: FmocOSu, Na₂CO₃ aq., dioxane

5 *i, ii*: Typical procedures:

To a solution of 78 mmol of azides **210** and **215** in a (3:1)-mixture of dioxane/water (500 ml) was added at 0 °C SnCl₂ (59.2 g, 4 eq, 0.31 mol) and the solution was stirred for 30 minutes. The reaction mixture was gradually warmed up to room temperature and stirred for another 5 hours. After adjusting the pH to 8 with solid NaHCO₃, the reaction mixture was extracted with CH₂Cl₂, the organic fraction dried (MgSO₄), evaporated and the residue dried under reduced pressure. The residue was dissolved in CH₂Cl₂ (300ml), cooled to 4° with an ice bath, followed by addition of DIEA (20.0ml, 117mmol) and a solution of the appropriate acid chloride R^{64'}COCl (101.0mmol) in CH₂Cl₂ (50ml) at 4°C. The reaction mixture was stirred for 1 hour at 4° and for 18 hours at room temperature and extracted with HCl aq. (0.5N, 200ml) and CH₂Cl₂. The organic fraction was dried (MgSO₄), evaporated and the residue chromatographed on SiO₂ with gradients of ethylacetate/hexane yielding **218a-u** and **220a-u**, which were converted into the final products **219a-u** and **221a-u** as described for the conversion of **216** into **217**. The overall yields were 50-60%.

Templates (b1):

- 5 Synthesis of (2*S*,6*S*,8*aR*)-8a-{{[(tert.-butyl)oxycarbonyl]methyl}perhydro-5,8-dioxo-{{[(9H-fluoren-9-yl)methoxycarbonyl]amino}-pyrrolo[1,2-a]pyrazine-6-acetic acid (222):

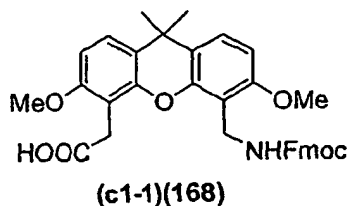


- 10 To a stirred solution of 250mg (0.414mmol) of allyl {(2*S*,6*S*,8*aR*)-8a-[(tert.-butyl)oxycarbonyl] methyl}perhydro-5,8-dioxo-{{[(9H-fluoren-9-yl)methoxycarbonyl]amino}-pyrrolo[1,2-a]pyrazine-6-acetate in a degassed mixture of dichloromethane/methanol (9:1, 3ml) were added under argon 25mg (0.0216mmol) of tetrakis(triphenylphosphine)palladium, 0.05ml of acetic acid and 0.025ml of *N*-methylmorpholine. The reaction mixture was stirred for 48 hours at room temperature and poured onto water and dichloromethane. The organic phase was dried (MgSO₄), evaporated and the residue chromatographed on SiO₂ with
- 15 dichloromethane/methanol (9:1) to yield 180mg (77%) of (2*S*,6*S*,8*aR*)-8a-{{[(tert.-butyl)oxycarbonyl]methyl}perhydro-5,8-dioxo-{{[(9H-fluoren-9-yl)-methoxycarbonyl]amino}-pyrrolo[1,2-a]pyrazine-6-acetic acid (222) as a white powder.

- 20 ¹H-NMR(300MHz, DMSO-d₆): 8.30 (s, 1H); 7.88 (d, J= 7.2, 2H); 7.67 (d, J=7.4, 2H); 7.62 (br.s, 1H); 7.41 (t, J= 7.2, 2H); 7.33 (t, J=7.4, 2H); 4.35-4.2 (m, 5H); 3.55 (br.d, J= 6.3, 2H); 2.8-2.55 (m, 3H); 2.45-2.25 (m, 2H); 2.1-1.95 (m, 1H); 1.35 (s, 9H); MS(ESI): 586.1 (M+Na)⁺, 564.1 (M+H)⁺.

Templates (c1):

25



Experimental procedure described in W. Bannwarth, A. Knierzinger, K. Müller, D. Obrecht, A. Trzeciak, EP 0 592 791 A2, 1993.

3. Biological methods

3.1. Preparation of the peptides.

- 5 Lyophilized peptides were weighed on a Microbalance (Mettler MT5) and dissolved in sterile water containing 0.01% acetic acid. Tachyplesin was purchased from *Bachem Ltd.* (Bubendorf Switzerland).

3.2. Antimicrobial activity of the peptides.

10

- The antimicrobial activities of the peptides were determined by the standard NCCLS broth microdilution method (see ref 1, below) examined in sterile 96-wells plates (Nunclon polystyrene microtiter plates) in a total volume of 100 µl. Inocula of the microorganisms were prepared with 0.5 Mcfarland standard and then diluted into Mueller-Hinton (MH) broth to give appr. 10^6 colony forming units (CFU)/ml for bacteria or 5×10^3 CFU/ml for *Candida*. Aliquots (50 µl) of the inocula were added to 50 µl of MH broth containing the peptide in serial twofold dilutions. The microorganisms used were *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (*P. aeruginosa*) (ATCC 27853), *Staphylococcus aureus* (ATCC 29213 and ATCC 25923) and *Candida albicans*. A selected number of peptides were
20 screened for activity against a larger panel of gram-negative strains. These strains were; *Escherichia coli* ATCC 43827 and clinical isolates of *Pseudomonas* (*P. aeruginosa* VO7 14482, *P. aeruginosa* 15288, *P. aeruginosa* V02 15328 and *P. aeruginosa* V09 16085) and *Acinetobacter* (*Acinetobacter* V04 19905/1, *Acinetobacter* V12 21143/1 and *Acinetobacter* V12 21193/1). Antimicrobial activities of the peptides were expressed as the minimal
25 inhibitory concentration (MIC) in µg/ml at which no visible growth was observed after 18-20 hours of incubation of the microtiter plates at 37°C.

3.3. Antimicrobial activity of the peptides in 1% Salt

- 30 Salt sensitivity of the peptides was tested by the microtiter serial dilution assay as described above. Only MH broth was replaced by MH broth containing 1 % NaCl.

3.4. Antimicrobial activity of the peptides in Human serum

- 35 Serum binding of the peptides was tested by microtiter serial dilution assay as described above. Only MH broth was replaced by MH broth containing 90% human serum (BioWhittaker).

3.5. Hemolysis

5 The peptides were tested for their hemolytic activity against human red blood cells (hRBC). Fresh hRBC were washed three times with phosphate buffered saline (PBS) by centrifugation for 10 min at 2000 x g. Peptides at a concentration of 100 µg/ml were incubated with 20% v/v hRBC for 1 hour at 37°C. The final erythrocyte concentration was appr. 0.9×10^9 /ml. A value of 0% resp. 100% cell lysis was determined by incubation of the hRBC in the presence of PBS alone and resp. 0.1% Triton X-100 in H₂O. The samples were centrifuged and the supernatant was 20 fold diluted in PBS buffer and the optical density (OD) of the sample at 540 nm was measured. The 100% lysis value (OD_{540H20}) gave an OD of approximately 1.6-2.0. Percent hemolysis was calculated as follows: $(OD_{540\text{peptide}}/OD_{540H20}) \times 100\%$.

15 3.6. Cytotoxicity assay

The cytotoxicity of the peptides to HELA cells (Acc57) and MCF-7 cells (Acc115) was determined using the MTT reduction assay (see ref 2 and 3, below). Briefly the method is as follows; HELA cells and MCF-7 cells were grown in RPMI1640 plus 5% fetal calf serum in microtiter plates for 48 hours at 37°C at 5% CO₂. The total number of cells was finally 10^6 cells per well. The supernatant of the cell cultures was discarded and fresh RPMI1640 medium containing 5% fetal calf serum and the peptides in serial dilutions of 12.5, 25 and 50 µg/ml were pipeted into the wells. Each peptide concentration was assayed in triplicate. Incubation of the cells was continued for 20-24 hours at 37°C at 5% CO₂. Wells were then washed three times with fresh RPMI medium and finally 100 µl MTT reagent (0.5 mg/ml in RPMI1640) was added to each well. This was incubated at 37°C for 2 hours and subsequently the wells were washed once with PBS. 100 µl isopropanol was added to each well and the absorbance at 595 nm of the solubilized product was measured (OD_{595peptide}). The 100 percent growth value (OD_{595Medium}) was determined from wells containing HELA or MCF-7 cells with RPMI1640 plus 5% fetal calf serum but no peptides. The zero percent growth value (OD_{595Empty well}) was extracted from wells that did not contain HELA or MCF-7 cells. The percentage MTT reduction for a certain peptide concentration was calculated as follows: $(OD_{595\text{peptide}} - OD_{595\text{Empty well}}) / (OD_{595\text{Medium}} - OD_{595\text{Empty well}}) \times 100\%$ and was plotted for each peptide concentration. The EC₅₀ of a peptide is defined as the concentration at which 50% inhibition of MTT reduction was observed and was calculated for each peptide.

References

1. National Committee for Clinical Laboratory Standards. 1993. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, 3rd ed. Approved standard M7-A3. National Committee for Clinical laboratory standards, Villanova, Pa.
2. Mossman T. J Immunol Meth 1983, 65, 55-63
3. Berridge MV, Tan AS. *Archives of Biochemistry & Biophysics* 1993, 303, 474-482

10

3.7. Results

Table 8. Minimal inhibitory concentrations (MIC in $\mu\text{g/ml}$) and percentage hemolyses at a concentration of 100 $\mu\text{g/ml}$ of peptide

15

Ex.	<i>Escherichia coli</i> ATCC 25922	<i>Pseudomonas putida</i> ATCC 27853	<i>Staphylococcus aureus</i> ATCC 29213	<i>Staphylococcus aureus</i> ATCC 25923	<i>Candida albicans</i>	Hemolyses hRBC
11	25	100	100	100	100	0.2
36	25	25	25	50	25	0.5
40	25	50	25	50	25	1.2
59	4.7	50	25	50	25	3.0
63	6.2	50	12.5	25	12.5	3.0
71	12.5	100	12.5	12.5	50	1.2
87	6.2	6.2	9.4	9.4	12.5	3.7
101	12.5	50	>50	>50	50	0.2
103	9.4	25	25	25	12.5	18.3
105	6.2	9.4	12.5	6.2	6.2	31.0
106	12.5	6.2	25	12.5	12.5	1.4
107	25	6.2	12.5	9.4	12.5	10.4
109	50	25	50	50	12.5	3.2
112	25	50	25	25	25	2.6
113	50	100	100	100	100	9.2
119	50	25	>100	100	50	3.5
120	18.8	9.4	18.8	9.4	12.5	1.1
121	25	25	6.2	6.2	6.2	7.1
126	25	25	25	50	25	2.6
128	6.2	12.5	6.2	6.2	12.5	13.9
133	6.2	6.2	12.5	25	12.5	1.1
134	12.5	6.2	12.5	25	12.5	1.2
137	25	6.2	6.2	6.2	6.2	3.1
139	25	6.2	12.5	9.4	6.2	3.5
140	12.5	6.2	12.5	12.5	6.2	2.7
141	25	12.5	25	25	12.5	2.0
142	25	12.5	50	25	12.5	2.3

Ex.	<i>Escherichia coli</i> ATCC 25922	<i>Pseudo- monas putida</i> ATCC 27853	<i>Staphylo- coccus aureus</i> ATCC 29213	<i>Staphylo- coccus aureus</i> ATCC 25923	<i>Candida albicans</i>	<i>Hemo- lyses hRBC</i>
146	12.5	12.5	25	12.5	6.2	30.1
147	50	25	25	25	12.5	1.9
148	25	12.5	12.5	9.4	6.2	3.9
150	25	12.5	12.5	12.5	12.5	29.3
151	50	50	100	50	25	4.9
152	25	25	50	25	12.5	29.1
154	12.5	12.5	25	12.5	12.5	31.5
155	6.2	12.5	6.2	12.5	6.2	10.1
156	50	12.5	12.5	6.2	12.5	35.2
158	12.5	6.2	12.5	12.5	12.5	10.5
159	12.5	12.5	12.5	12.5	12.5	21.7
161	25	12.5	6.2	6.2	12.5	3.7
163	12.5	12.5	12.5	12.5	12.5	24.6
165	6.2	12.5	25	18	12.5	0.2
168	12.5	12.5	25	25	12.5	1.1
172	6.2	25	25	25	12.5	1.0
173	12.5	25	6.2	12.5	12.5	27.4
175	12.5	6.2	12.5	12.5	12.5	2.4
177	25	12.5	25	25	12.5	4.1
182	12.5	6.2	6.2	25	12.5	6.2
185	12.5	6.2	6.2	6.2	12.5	17.6
186	6.2	3.1	6.2	6.2	6.2	11.5
187	12.5	100	50	100	25	0.3
197	12.5	3.1	6.2	6.2	6.2	3.4
203	6.2	6.2	6.2	6.2	6.2	33.0
205	6.2	6.2	12.5	6.2	6.2	27.0
206	6.2	6.2	12.5	12.5	6.2	8.5
207	50	50	25	50	25	0.1
208	12.5	6.2	6.2	6.2	12.5	18.4
209	12.5	6.2	12.5	12.5	18.8	6.4
210	12.5	6.2	25	25	25	1.9
214	12.5	6.2	12.5	12.5	12.5	1.0
216	12.5	6.2	12.5	25	12.5	1.4
217	18.8	6.2	12.5	25	12.5	1.7
218	25	6.2	25	25	25	2.2
219	12.5	12.5	50	50	25	2.6
220	12.5	18.8	25	25	12.5	2.3
222	12.5	6.2	12.5	12.5	6.2	2.2
223	6.2	12.5	12.5	25	12.5	2.7
224	6.2	12.5	18.8	25	12.5	3.7
225	6.2	12.5	12.5	25	12.5	4.4
228	12.5	6.2	6.2	6.2	12.5	6.3
229	12.5	6.2	3.1	6.2	6.2	4.8

Ex.	<i>Escherichia coli</i> ATCC 25922	<i>Pseudomonas putida</i> ATCC 27853	<i>Staphylococcus aureus</i> ATCC 29213	<i>Staphylococcus aureus</i> ATCC 25923	<i>Candida albicans</i>	Hemolyses hRBC
230	6.2	6.2	6.2	9.4	12.5	1.7
232	6.2	12.5	9.4	6.2	9.4	1.5
233	9.4	12.5	9.4	6.2	12.5	37
234	6.2	12.5	6.2	3.1	12.5	33.9
242	6.2	12.5	6.2	12.5	12.5	19.4
244	3.1	12.5	6.2	6.2	12.5	22.7
250	6.2	6.2	12.5	12.5	12.5	0.7
251	6.2	9.4	6.2	12.5	12.5	4.1
254	12.5	6.2	6.2	12.5	12.5	11.7
256	3.1	3.1	6.2	6.2	6.2	2.7
257	6.2	6.2	6.2	6.2	25	19.6
258	6.2	6.2	6.2	6.2	12.5	23.6
259	6.2	6.2	6.2	6.2	12.5	18.0
267	12.5	6.2	6.2	12.5	12.5	3.4
277	25	18.8	3.1	6.2	6.2	12.7
278	12.5	25	50	50	50	5.3
279	12.5	12.5	50	50	50	4.9
280	12.5	12.5	50	100	25	1.8
281	12.5	4.7	100	100	50	1.1
282	12.5	12.5	25	50	25	1.6
283	12.5	4.7	100	100	50	1.0
284	6.2	1.6	12.5	12.5	12.5	0.7
287	25	50	12.5	25	25	28.5
288	25	1.5	100	100	100	1.1
289	50	3.1	25	25	25	1.7
292	25	6.2	50	100	25	1.3
293	25	12.5	100	100	100	1.3
294	25	3.1	100	100	50	1.5
295	25	6.5	50	100	50	2.0
296	12.5	6.2	25	50	25	1.9
297	25	3.1	100	100	50	0.9
298	25	3.1	100	200	50	1.0
299	50	6.2	25	100	50	2.5
300	25	12.5	12.5	25	50	6.5
301	25	50.0	50.0	25	50.0	0.5
302	6.2	3.1	3.1	6.2	6.2	3.4

Table 9. Minimal inhibitory concentration (MIC in $\mu\text{g/ml}$) in Mueller-Hinton broth containing 1% NaCl

Ex.	<i>Escherichia coli</i> ATCC 25922	<i>Pseudomonas putida</i> ATCC 27853	<i>Staphylococcus aureus</i> ATCC 29213	<i>Staphylococcus aureus</i> ATCC 25923	<i>Candida albicans</i>
106	100	50	100	100	100
197	12.5	6.2	18.8	12.5	12.5
230	25	50	50	50	18.8
250	12.5	50	100	50	50
229	50	18.8	25	25	12.5
256	6.2	6.2	25	25	25

5

Several compounds which showed a preference towards Gram-negative bacteria were tested against several pseudomonas strains as shown in Table 10.

Table 10. Minimal inhibitory concentrations (MIC in $\mu\text{g/ml}$) against pseudomonas strains

10

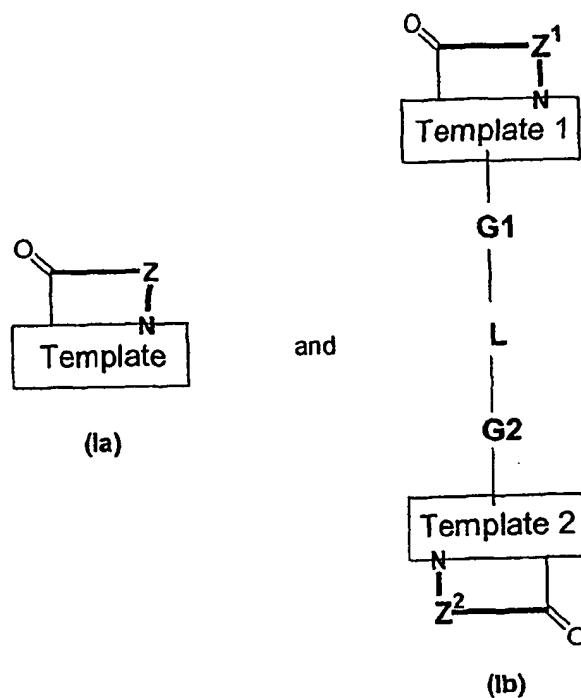
MIC ($\mu\text{g/ml}$)	ex.197	ex.284	ex.283	ex.288	ex.289	ex.292	ex.296	ex.297	ex.298
<i>Escherichia coli</i> ATCC 25922	12.5	6.2	25	25	25	25	12.5	25	25
<i>Escherichia coli</i> ATCC 43827	12.5	12.5	12.5	12.5	25	25	12.5	12.5	12.5
<i>P. aeruginosa</i> ATCC 278853	3.1	1.6	3.1	3.1	6.2	6.2	3.1	3.1	3.1
<i>P. aeruginosa</i> VO7 14482	12.5	3.1	4.7	3.1	6.2	12.5	12.5	4.7	3.1
<i>P. aeruginosa</i> 15288	12.5	3.1	25	6.2	6.2	12.5	12.5	6.2	4.7
<i>P. aeruginosa</i> V02 15328	12.5	3.1	6.2	3.1	6.2	12.5	12.5	6.2	3.1
<i>P. aeruginosa</i> V09 16085	9.4	1.6	3.1	6.2	6.2	6.2	6.2	3.1	3.1
<i>Acinetobacter</i> V04 19905/1	12.5	6.2	6.2	6.2	12.5	12.5	6.2	6.2	6.2
<i>Acinetobacter</i> V12 21143/1	12.5	3.1	6.2	6.2	6.2	6.2	6.2	6.2	9.4
<i>Acinetobacter</i> V12 21193/1	12.5	3.1	3.1	6.2	3.1	6.2	3.1	6.2	6.2

Table 11: Anticancer activity (EC₅₀-values) in µg/ml

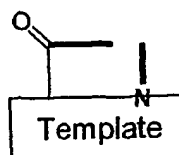
Example ex.	Hela (µg/ml)	MCF (µg/ml)	Hemolysis hRBC
80	337	nd	nd
106	43	39	1.4
170	24	41	nd
197	20	23	3.4
229	13	25	4.8
230	23	32	1.7
285	11	11	4.2
286	nd	23	17.1

CLAIMS

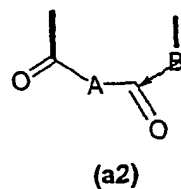
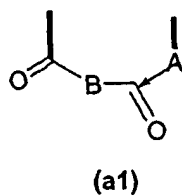
1. Compounds of the general formulae



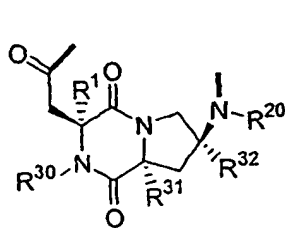
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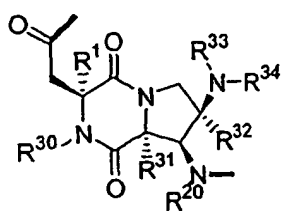
wherein



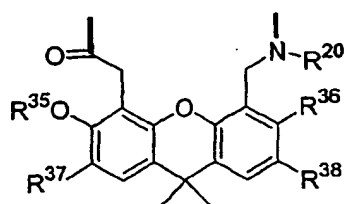
10 is a group of one of the formulae



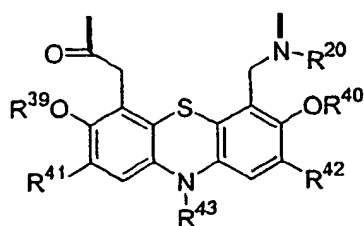
(b1)



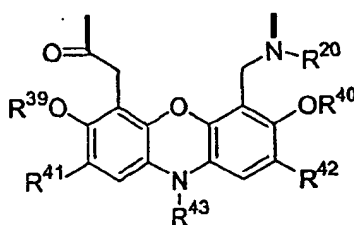
(b2)



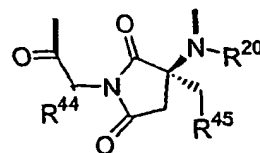
(c1)



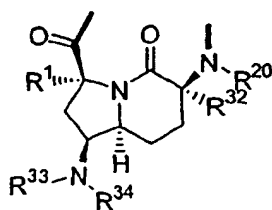
(c2)



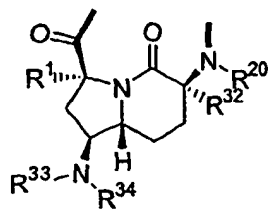
(c3)



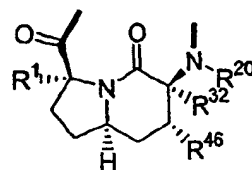
(d)



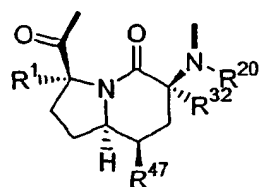
(e1)



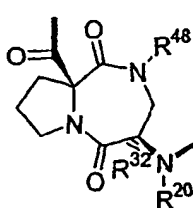
(e2)



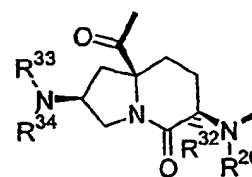
(e3)



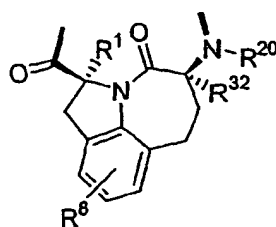
(e4)



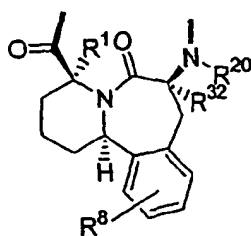
(f)



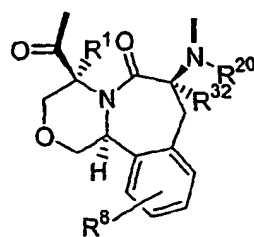
(g)



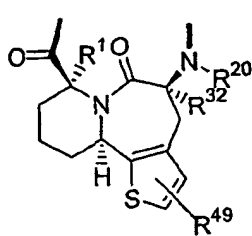
(h)



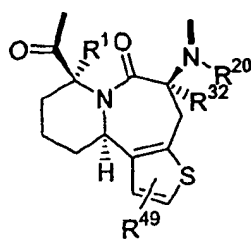
(i1)



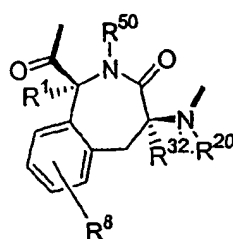
(i2)



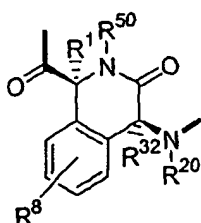
(i3)



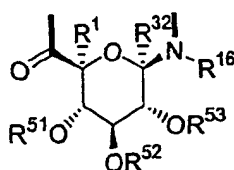
(i4)



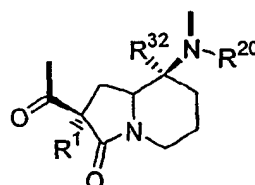
(i)



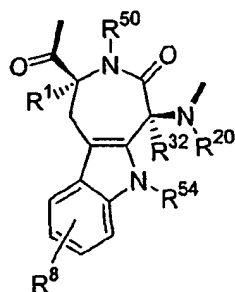
(k)



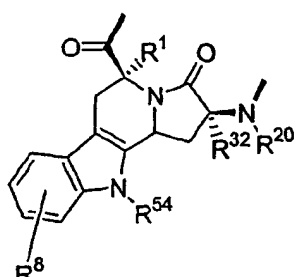
(l)



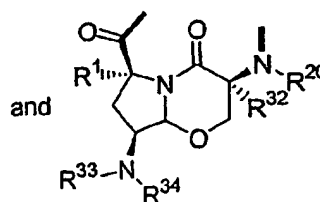
(m)



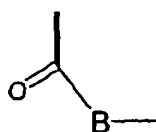
(n)



(o)



(p)

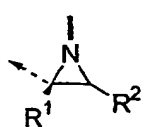


wherein

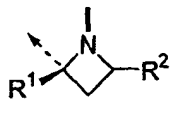
- 5 is the residue of an L- α -amino acid with B being a residue of formula $-\text{NR}^{20}\text{CH}(\text{R}^{71})-$ or the enantiomer of one of the groups A1 to A69 as defined hereinafter;



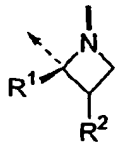
is a group of one of the formulae



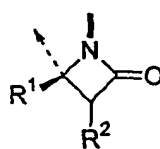
A1



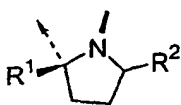
A2



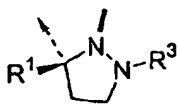
A3



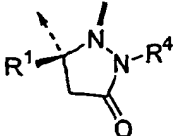
A4



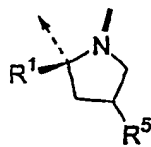
A5



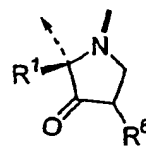
A6



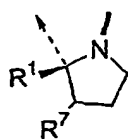
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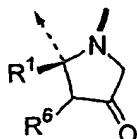
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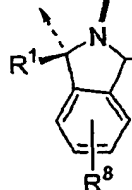
A9



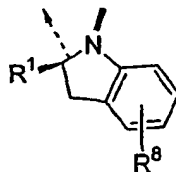
A10



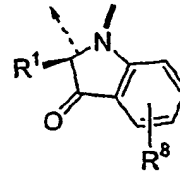
A11



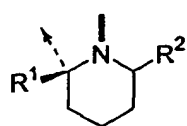
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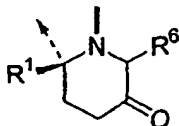
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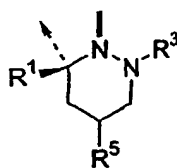
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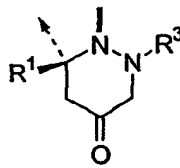
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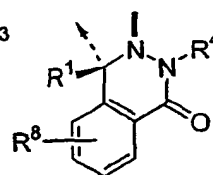
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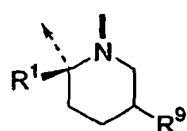
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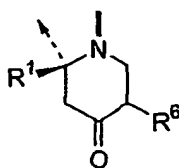
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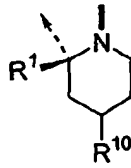
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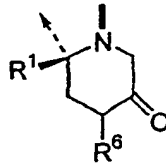
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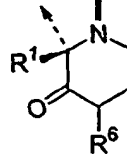
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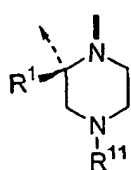
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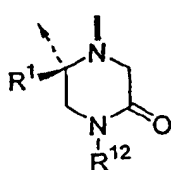
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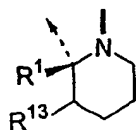
A24



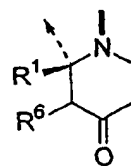
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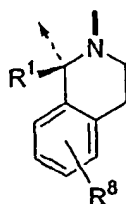
A26



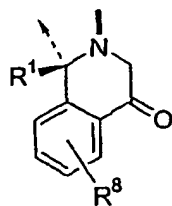
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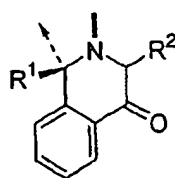
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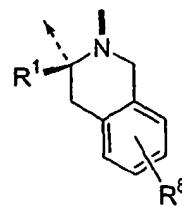
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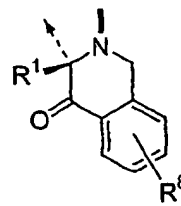
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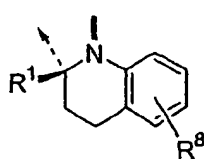
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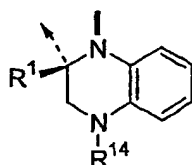
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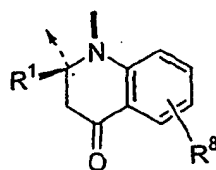
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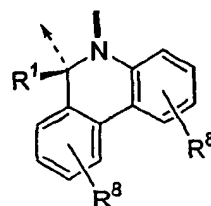
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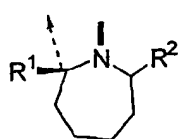
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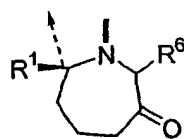
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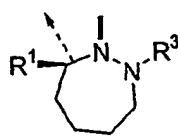
A37



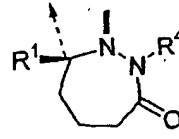
A38



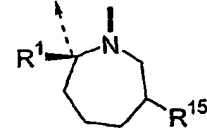
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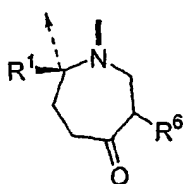
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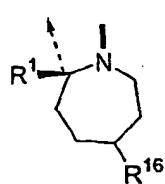
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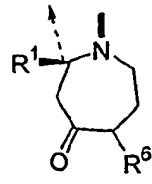
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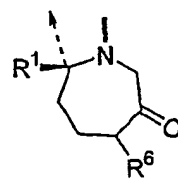
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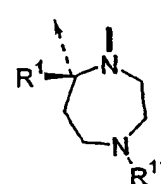
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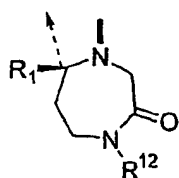
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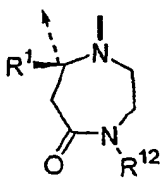
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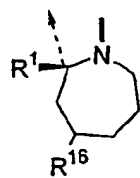
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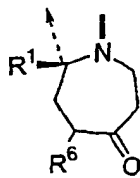
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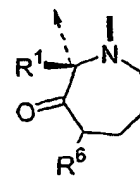
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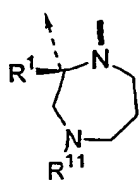
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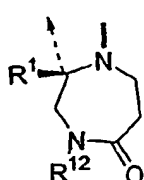
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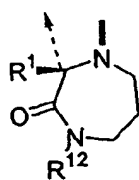
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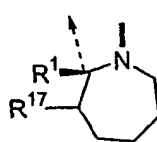
A53



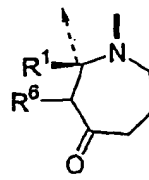
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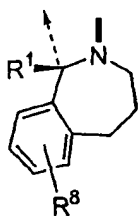
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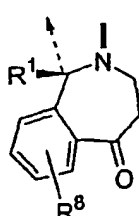
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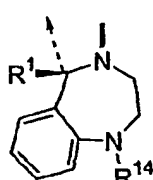
A57



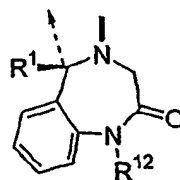
A58



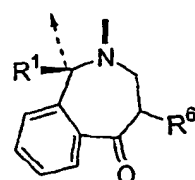
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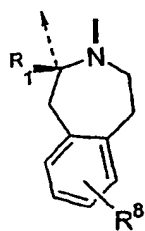
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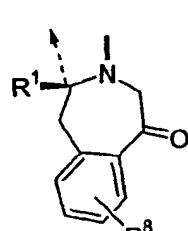
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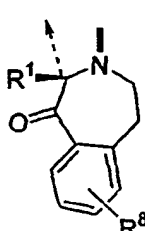
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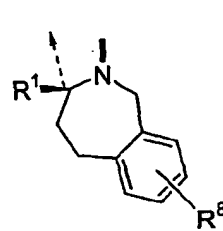
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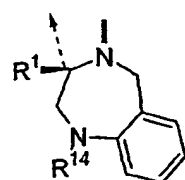
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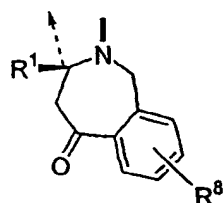
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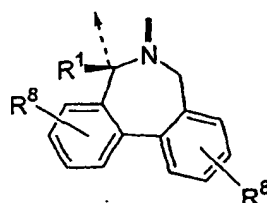
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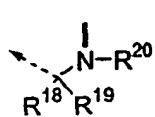
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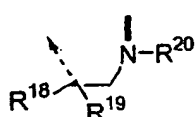
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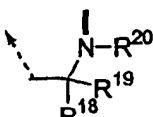
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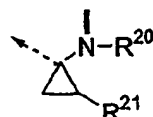
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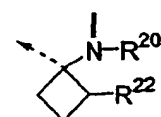
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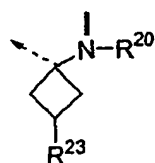
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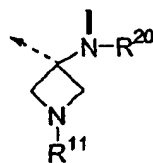
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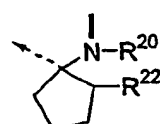
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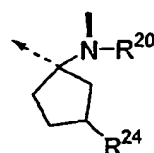
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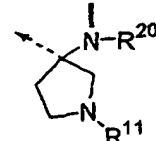
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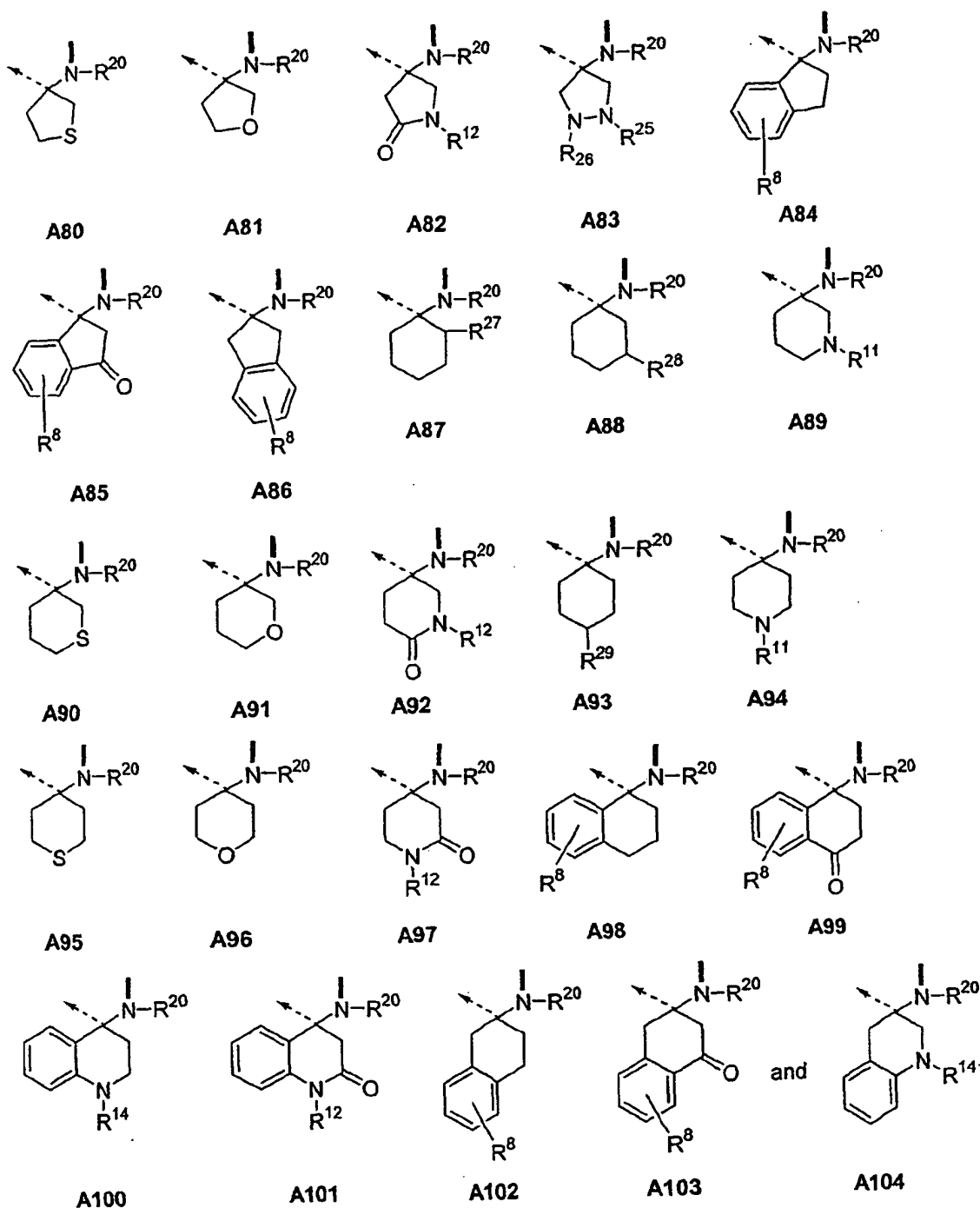
A77



A78



A79



R¹ is H; lower alkyl; or aryl-lower alkyl;

R² is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sSR^{56}$;
 $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$;
 $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sCOOR^{57}$;
 $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R³ is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sSR^{56}$;

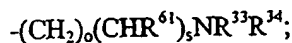
- $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$;
 $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sCOOR^{57}$;
 $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
5 R^4 is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sSR^{56}$;
 $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_p(CHR^{61})_sCOOR^{57}$; $-(CH_2)_p(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_p(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_p(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
10 R^5 is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R^6 is H; alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$;
15 $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R^7 is alkyl; alkenyl; $-(CH_2)_q(CHR^{61})_sOR^{55}$; $-(CH_2)_q(CHR^{61})_sNR^{33}R^{34}$;
20 $-(CH_2)_q(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_q(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_r(CHR^{61})_sCOOR^{57}$; $-(CH_2)_r(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_r(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_r(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_r(CHR^{61})_sC_6H_4R^8$;
 R^8 is H; Cl; F; CF_3 ; NO_2 ; lower alkyl; lower alkenyl; aryl; aryl-lower alkyl;
 $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
25 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sCOR^{64}$;
 R^9 is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
30 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R^{10} is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$;
 $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
35 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R^{11} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$;

- $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R¹² is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sSR^{56}$;
 5 $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$;
 $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_m(CHR^{61})_sCOOR^{57}$; -
 $(CH_2)_m(CHR^{61})_sCONR^{58}R^{59}$;
 $-(CH_2)_m(CHR^{61})_sPO(OR^{60})_2$; $-(CH_2)_m(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_m(CHR^{61})_sC_6H_4R^8$;
 R¹³ is alkyl; alkenyl; $-(CH_2)_q(CHR^{61})_sOR^{55}$; $-(CH_2)_q(CHR^{61})_sSR^{56}$; $-(CH_2)_q(CHR^{61})_sNR^{33}R^{34}$;
 10 $-(CH_2)_q(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_q(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_q(CHR^{61})_sCOOR^{57}$; $-(CH_2)_q(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_q(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_q(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_q(CHR^{61})_sC_6H_4R^8$;
 R¹⁴ is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 15 $-(CH_2)_q(CHR^{61})_sCOOR^{57}$; $-(CH_2)_q(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_q(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_q(CHR^{61})_sSOR^{62}$; or $-(CH_2)_q(CHR^{61})_sC_6H_4R^8$;
 R¹⁵ is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 20 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R¹⁶ is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 25 R¹⁷ is alkyl; alkenyl; $-(CH_2)_q(CHR^{61})_sOR^{55}$; $-(CH_2)_q(CHR^{61})_sSR^{56}$; $-(CH_2)_q(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_q(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_q(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_q(CHR^{61})_sCOOR^{57}$; $-(CH_2)_q(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_q(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_q(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_q(CHR^{61})_sC_6H_4R^8$;
 R¹⁸ is alkyl; alkenyl; $-(CH_2)_p(CHR^{61})_sOR^{55}$; $-(CH_2)_p(CHR^{61})_sSR^{56}$; $-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$;
 30 $-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_p(CHR^{61})_sCOOR^{57}$; $-(CH_2)_p(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_p(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_p(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_p(CHR^{61})_sC_6H_4R^8$;
 R¹⁹ is lower alkyl; $-(CH_2)_p(CHR^{61})_sOR^{55}$; $-(CH_2)_p(CHR^{61})_sSR^{56}$; $-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$;
 $-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 35 $-(CH_2)_p(CHR^{61})_sCOOR^{57}$; $-(CH_2)_p(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_p(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_p(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_p(CHR^{61})_sC_6H_4R^8$; or
 R¹⁸ and R¹⁹ taken together can form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or

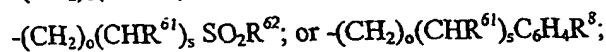
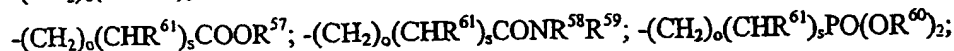


R^{20} is H; alkyl; alkenyl; or aryl-lower alkyl;

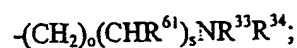
R^{21} is H; alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$;



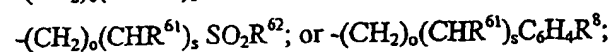
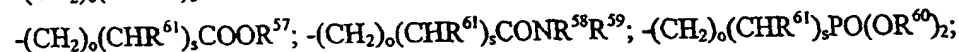
5 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;



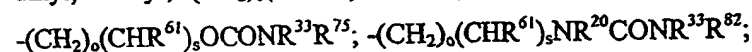
R^{22} is H; alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$;



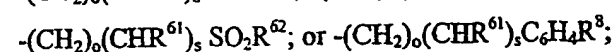
10 $-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;



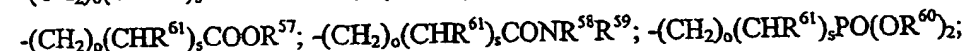
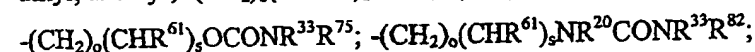
R^{23} is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;



15 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;

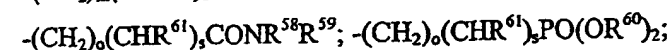
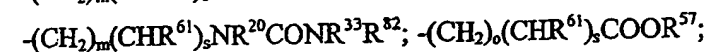
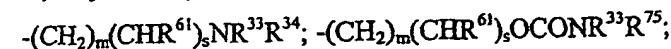


R^{24} is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$; $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;



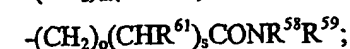
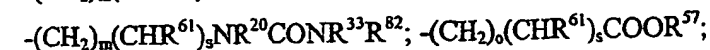
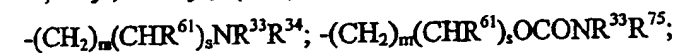
20 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}; \text{ or } -(CH_2)_o(CHR^{61})_sC_6H_4R^8;$

R^{25} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sSR^{56}$;



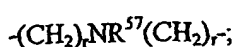
25 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}; \text{ or } -(CH_2)_o(CHR^{61})_sC_6H_4R^8;$

R^{26} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sSR^{56}$;

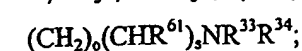


30 $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$; $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$; or

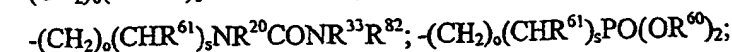
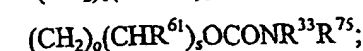
R^{25} and R^{26} taken together can form: $-(CH_2)_{2-6}-$; $-(CH_2)_rO(CH_2)_r-$; $-(CH_2)_rS(CH_2)_r-$; or



R^{27} is H; alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$; -



35 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; -



- $-(CH_2)_o(CHR^{61})_s SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_s C_6H_4R^8$;
 R^{28} is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_s OR^{55}$; $-(CH_2)_o(CHR^{61})_s SR^{56}$; $-(CH_2)_o(CHR^{61})_s$
 $NR^{33}R^{34}$;
 $-(CH_2)_o(CHR^{61})_s OCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_s NR^{20}CONR^{33}R^{82}$;
5 $-(CH_2)_o(CHR^{61})_s COOR^{57}$; $-(CH_2)_o(CHR^{61})_s CONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_s PO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_s SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_s C_6H_4R^8$;
 R^{29} is alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_s OR^{55}$; $-(CH_2)_o(CHR^{61})_s SR^{56}$; $-(CH_2)_o(CHR^{61})_s NR^{33}R^{34}$;
 $-(CH_2)_o(CHR^{61})_s OCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_s NR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_s COOR^{57}$; $-(CH_2)_o(CHR^{61})_s CONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_s PO(OR^{60})_2$;
10 $-(CH_2)_o(CHR^{61})_s SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_s C_6H_4R^8$;
 R^{30} is H; alkyl; alkenyl; or aryl-lower alkyl;
 R^{31} is H; alkyl; alkenyl; $-(CH_2)_p(CHR^{61})_s OR^{55}$; $-(CH_2)_p(CHR^{61})_s NR^{33}R^{34}$;
 $-(CH_2)_p(CHR^{61})_s OCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_s NR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_s COOR^{57}$; $-(CH_2)_o(CHR^{61})_s CONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_s PO(OR^{60})_2$;
15 $-(CH_2)_o(CHR^{61})_s SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_s C_6H_4R^8$;
 R^{32} is H; lower alkyl; or aryl-lower alkyl;
 R^{33} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_s OR^{55}$; $-(CH_2)_m(CHR^{61})_s NR^{34}R^{63}$;
 $-(CH_2)_m(CHR^{61})_s OCONR^{75}R^{82}$; $-(CH_2)_m(CHR^{61})_s NR^{20}CONR^{78}R^{82}$;
 $-(CH_2)_o(CHR^{61})_s COR^{64}$; $-(CH_2)_o(CHR^{61})_s CONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_s PO(OR^{60})_2$;
20 $-(CH_2)_o(CHR^{61})_s SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_s C_6H_4R^8$;
 R^{34} is H; lower alkyl; aryl, or aryl-lower alkyl;
 R^{33} and R^{34} taken together can form: $-(CH_2)_2-6-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or
 $-(CH_2)_2NR^{57}(CH_2)_2-$;
 R^{35} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_s OR^{55}$; $-(CH_2)_m(CHR^{61})_s NR^{33}R^{34}$;
25 $-(CH_2)_m(CHR^{61})_s OCONR^{33}R^{75}$; $-(CH_2)_m(CHR^{61})_s NR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_p(CHR^{61})_s COOR^{57}$; $-(CH_2)_p(CHR^{61})_s CONR^{58}R^{59}$; $-(CH_2)_p(CHR^{61})_s PO(OR^{60})_2$;
 $-(CH_2)_p(CHR^{61})_s SO_2R^{62}$; or $-(CH_2)_p(CHR^{61})_s C_6H_4R^8$;
 R^{36} is H; alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_s OR^{55}$; $-(CH_2)_p(CHR^{61})_s NR^{33}R^{34}$;
 $-(CH_2)_p(CHR^{61})_s OCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_s NR^{20}CONR^{33}R^{82}$;
30 $-(CH_2)_p(CHR^{61})_s COOR^{57}$; $-(CH_2)_p(CHR^{61})_s CONR^{58}R^{59}$; $-(CH_2)_p(CHR^{61})_s PO(OR^{60})_2$;
 $-(CH_2)_p(CHR^{61})_s SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_s C_6H_4R^8$;
 R^{37} is H; F; Br; Cl; NO_2 ; CF_3 ; lower alkyl; $-(CH_2)_p(CHR^{61})_s OR^{55}$; $-(CH_2)_p(CHR^{61})_s NR^{33}R^{34}$;
 $-(CH_2)_p(CHR^{61})_s OCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_s NR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_s COOR^{57}$; $-(CH_2)_o(CHR^{61})_s CONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_s PO(OR^{60})_2$;
35 $-(CH_2)_o(CHR^{61})_s SO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_s C_6H_4R^8$;
 R^{38} is H; F; Br; Cl; NO_2 ; CF_3 ; alkyl; alkenyl; $-(CH_2)_p(CHR^{61})_s OR^{55}$;
 $-(CH_2)_p(CHR^{61})_s NR^{33}R^{34}$;

$-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;
 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^{39} is H; alkyl; alkenyl; or aryl-lower alkyl;

5 R^{40} is H; alkyl; alkenyl; or aryl-lower alkyl;

R^{41} is H; F; Br; Cl; NO_2 ; CF_3 ; alkyl; alkenyl; $-(CH_2)_p(CHR^{61})_sOR^{55}$;

$-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$;

$-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;

$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;

10 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^{42} is H; F; Br; Cl; NO_2 ; CF_3 ; alkyl; alkenyl; $-(CH_2)_p(CHR^{61})_sOR^{55}$;

$-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$;

$-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;

$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;

15 $-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^{43} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$;

$-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;

$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;

$-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

20 R^{44} is alkyl; alkenyl; $-(CH_2)_l(CHR^{61})_sOR^{55}$; $-(CH_2)_l(CHR^{61})_sSR^{56}$; $-(CH_2)_l(CHR^{61})_sNR^{33}R^{34}$;

$-(CH_2)_l(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_l(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;

$-(CH_2)_l(CHR^{61})_sCOOR^{57}$; $-(CH_2)_l(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_l(CHR^{61})_sPO(OR^{60})_2$;

$-(CH_2)_l(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_l(CHR^{61})_sC_6H_4R^8$;

R^{45} is H; alkyl; alkenyl; $-(CH_2)_o(CHR^{61})_sOR^{55}$; $-(CH_2)_o(CHR^{61})_sSR^{56}$;

25 $-(CH_2)_o(CHR^{61})_sNR^{33}R^{34}$;

$-(CH_2)_o(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_o(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;

$-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_sPO(OR^{60})_2$;

$-(CH_2)_o(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;

R^{46} is H; alkyl; alkenyl; or $-(CH_2)_p(CHR^{61})_sC_6H_4R^8$;

30 R^{47} is H; alkyl; alkenyl; or $-(CH_2)_o(CHR^{61})_sOR^{55}$;

R^{48} is H; lower alkyl; lower alkenyl; or aryl-lower alkyl;

R^{49} is H; alkyl; alkenyl; $-(CHR^{61})_sCOOR^{57}$; $(CHR^{61})_sCONR^{58}R^{59}$; $(CHR^{61})_sPO(OR^{60})_2$;

$-(CHR^{61})_sSOR^{62}$; or $-(CHR^{61})_sC_6H_4R^8$;

R^{50} is H; lower alkyl; or aryl-lower alkyl;

35 R^{51} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sSR^{56}$;

$-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$;

$-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sCOOR^{57}$;

- $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_pPO(OR^{60})_2$;
 $-(CH_2)_p(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_p(CHR^{61})_sC_6H_4R^8$;
 R^{52} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sSR^{56}$;
 $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$;
5 $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sCOOR^{57}$;
 $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_pPO(OR^{60})_2$;
 $-(CH_2)_p(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_p(CHR^{61})_sC_6H_4R^8$;
 R^{53} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sSR^{56}$;
 $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$;
10 $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$;
 $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sCOOR^{57}$;
 $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; $-(CH_2)_o(CHR^{61})_pPO(OR^{60})_2$;
 $-(CH_2)_p(CHR^{61})_sSO_2R^{62}$; or $-(CH_2)_p(CHR^{61})_sC_6H_4R^8$;
 R^{54} is H; alkyl; alkenyl; $-(CH_2)_m(CHR^{61})_sOR^{55}$; $-(CH_2)_m(CHR^{61})_sNR^{33}R^{34}$;
15 $-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_o(CHR^{61})_sCOOR^{57}$; $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$; or $-(CH_2)_o(CHR^{61})_sC_6H_4R^8$;
 R^{55} is H; lower alkyl; lower alkenyl; aryl-lower alkyl; $-(CH_2)_m(CHR^{61})_sOR^{57}$;
 $-(CH_2)_m(CHR^{61})_sNR^{34}R^{63}$; $-(CH_2)_m(CHR^{61})_sOCONR^{75}R^{82}$;
 $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{78}R^{82}$; $-(CH_2)_o(CHR^{61})_s-COR^{64}$; $-(CH_2)_o(CHR^{61})_sCOOR^{57}$;
20 or
 $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
 R^{56} is H; lower alkyl; lower alkenyl; aryl-lower alkyl; $-(CH_2)_m(CHR^{61})_sOR^{57}$;
 $-(CH_2)_m(CHR^{61})_sNR^{34}R^{63}$; $-(CH_2)_m(CHR^{61})_sOCONR^{75}R^{82}$;
 $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{78}R^{82}$; $-(CH_2)_o(CHR^{61})_s-COR^{64}$; or
25 $-(CH_2)_o(CHR^{61})_sCONR^{58}R^{59}$;
 R^{57} is H; lower alkyl; lower alkenyl; aryl lower alkyl; or heteroaryl lower alkyl;
 R^{58} is H; lower alkyl; lower alkenyl; aryl; heteroaryl; aryl-lower alkyl; or heteroaryl-lower
alkyl;
 R^{59} is H; lower alkyl; lower alkenyl; aryl; heteroaryl; aryl-lower alkyl; or heteroaryl-lower
30 alkyl; or
 R^{58} and R^{59} taken together can form: $-(CH_2)_2-6-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or
 $-(CH_2)_2NR^{57}(CH_2)_2-$;
 R^{60} is H; lower alkyl; lower alkenyl; aryl; or aryl-lower alkyl;
 R^{61} is alkyl; alkenyl; aryl; heteroaryl; aryl-lower alkyl; heteroaryl-lower alkyl; $-(CH_2)_mOR^{55}$;
35 $-(CH_2)_mNR^{33}R^{34}$; $-(CH_2)_mOCONR^{75}R^{82}$; $-(CH_2)_mNR^{20}CONR^{78}R^{82}$; $-(CH_2)_oCOOR^{37}$;
 $-(CH_2)_oNR^{58}R^{59}$; or $-(CH_2)_oPO(COR^{60})_2$;
 R^{62} is lower alkyl; lower alkenyl; aryl; heteroaryl; or aryl-lower alkyl;

R^{63} is H; lower alkyl; lower alkenyl; aryl, heteroaryl; aryl-lower alkyl; heteroaryl-lower alkyl;

$-\text{COR}^{64}$; $-\text{COOR}^{57}$; $-\text{CONR}^{58}\text{R}^{59}$; $-\text{SO}_2\text{R}^{62}$; or $-\text{PO}(\text{OR}^{60})_2$;

R^{34} and R^{63} taken together can form: $-(\text{CH}_2)_{2-6}-$; $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2-$; $-(\text{CH}_2)_2\text{S}(\text{CH}_2)_2-$; or

5 $-(\text{CH}_2)_2\text{NR}^{57}(\text{CH}_2)_2-$;

R^{64} is H; lower alkyl; lower alkenyl; aryl; heteroaryl; aryl-lower alkyl; heteroaryl-lower alkyl;

$-(\text{CH}_2)_p(\text{CHR}^{61})_s\text{OR}^{65}$; $-(\text{CH}_2)_p(\text{CHR}^{61})_s\text{SR}^{66}$; or $-(\text{CH}_2)_p(\text{CHR}^{61})_s\text{NR}^{34}\text{R}^{63}$;

$-(\text{CH}_2)_p(\text{CHR}^{61})_s\text{OCONR}^{75}\text{R}^{82}$; $-(\text{CH}_2)_p(\text{CHR}^{61})_s\text{NR}^{20}\text{CONR}^{78}\text{R}^{82}$;

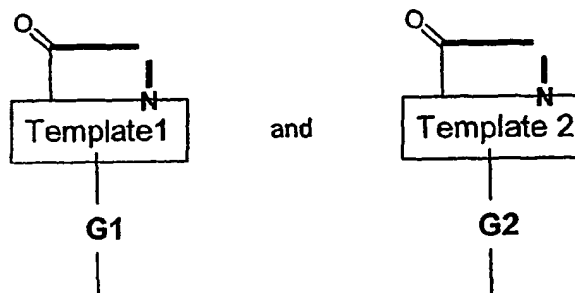
R^{65} is H; lower alkyl; lower alkenyl; aryl, aryl-lower alkyl; heteroaryl-lower alkyl; $-\text{COR}^{57}$;

10 $-\text{COOR}^{57}$; or $-\text{CONR}^{58}\text{R}^{59}$;

R^{66} is H; lower alkyl; lower alkenyl; aryl; aryl-lower alkyl; heteroaryl-lower alkyl; or

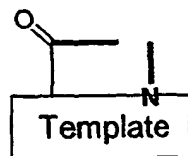
$-\text{CONR}^{58}\text{R}^{59}$;

m is 2-4; o is 0-4; p is 1-4; q is 0-2; r is 1 or 2; s is 0 or 1;



15

independently have any of the significances defined above for



except (a1) and (a2) with B being $-\text{NR}^{20}\text{CH}(\text{R}^{71})-$ and with A being A80, A81, A90, A91,

A95 or A96, and except (f) and (m), but wherein

20 R^2 is $-(\text{CH}_2)_m(\text{CHR}^{61})_s\text{O}-$; $-(\text{CH}_2)_m(\text{CHR}^{61})_s\text{S}-$; $-(\text{CH}_2)_m(\text{CHR}^{61})_s\text{NR}^{34}-$; or $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{CO}-$;

R^3 is $-(\text{CH}_2)_m(\text{CHR}^{61})_s\text{O}-$; $-(\text{CH}_2)_m(\text{CHR}^{61})_s\text{S}-$; $-(\text{CH}_2)_m(\text{CHR}^{61})_s\text{NR}^{34}-$; or $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{CO}-$;

R^4 is $-(\text{CH}_2)_m(\text{CHR}^{61})_s\text{O}-$; $-(\text{CH}_2)_m(\text{CHR}^{61})_s\text{S}-$; $-(\text{CH}_2)_m(\text{CHR}^{61})_s\text{NR}^{34}-$; or

25 $-(\text{CH}_2)_p(\text{CHR}^{61})_s\text{CO}-$;

R^5 is $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{O}-$; $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{S}-$; $-(\text{CH}_2)_o(\text{CHR}^{61})_s\text{NR}^{34}-$; or

- $-(CH_2)_o(CHR^{61})_sCO-$;
 R^6 is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or
 $-(CH_2)_o(CHR^{61})_sCO-$;
 R^7 is $-(CH_2)_q(CHR^{61})_sO-$; $-(CH_2)_q(CHR^{61})_sNR^{34}-$; or $-(CH_2)_r(CHR^{61})_sCO-$;
5 R^8 is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or
 $-(CH_2)_o(CHR^{61})_sCO-$;
 R^9 is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or
 $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{10} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or
10 $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{11} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{12} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_r(CHR^{61})_sCO-$;
 R^{13} is $-(CH_2)_q(CHR^{61})_sO-$; $-(CH_2)_q(CHR^{61})_sS-$; $-(CH_2)_q(CHR^{61})_sNR^{34}-$; or
 $-(CH_2)_q(CHR^{61})_sCO-$;
15 R^{14} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_q(CHR^{61})_sCO-$;
 R^{15} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or
 $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{16} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or
 $-(CH_2)_o(CHR^{61})_sCO-$;
20 R^{17} is $-(CH_2)_q(CHR^{61})_sO-$; $-(CH_2)_q(CHR^{61})_sS-$; $-(CH_2)_q(CHR^{61})_sNR^{34}-$; or
 $-(CH_2)_q(CHR^{61})_sCO-$;
 R^{18} is $-(CH_2)_p(CHR^{61})_sO-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sNR^{34}-$; or
 $-(CH_2)_p(CHR^{61})_sCO-$;
 R^{19} is $-(CH_2)_p(CHR^{61})_sO-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sNR^{34}-$; or
25 $-(CH_2)_p(CHR^{61})_sCO-$;
 R^{21} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or
 $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{22} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or
 $-(CH_2)_o(CHR^{61})_sCO-$;
30 R^{23} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or
 $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{24} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or
 $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{25} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or
35 $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{26} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or
 $-(CH_2)_o(CHR^{61})_sCO-$;

- R^{27} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{28} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;
5 R^{29} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{31} is $-(CH_2)_p(CHR^{61})_sO-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{33} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;
10 R^{37} is $-(CH_2)_p(CHR^{61})_sO-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{38} is $-(CH_2)_p(CHR^{61})_sO-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{41} is $-(CH_2)_p(CHR^{61})_sO-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;
15 R^{42} is $-(CH_2)_p(CHR^{61})_sO-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{43} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{45} is $-(CH_2)_o(CHR^{61})_sO-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sNR^{34}-$; or $-(CH_2)_s(CHR^{61})_sCO-$;
20 R^{47} is $-(CH_2)_o(CHR^{61})_sO-$;
 R^{49} is $-(CHR^{61})_sO-$; $-(CHR^{61})_sS-$; $-(CHR^{61})_sNR^{34}-$; or $-(CHR^{61})_sCO-$;
 R^{51} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;
25 R^{52} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{53} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{54} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;
30 R^{55} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{56} is $-(CH_2)_m(CHR^{61})_sO-$; $-(CH_2)_m(CHR^{61})_sNR^{34}-$; or $-(CH_2)_o(CHR^{61})_sCO-$;
 R^{64} is $-(CH_2)_p(CHR^{61})_sO-$; $-(CH_2)_p(CHR^{61})_sS-$; or $-(CH_2)_p(CHR^{61})_sNR^{34}-$;

m, o, p, q, r and s being as defined above;

with the proviso that if more than one of the substituents R^2 to R^{19} , R^{21} to R^{29} , R^{31} , R^{33} , R^{37} ,

- 35 R^{38} , R^{41} to R^{43} , R^{45} , R^{47} , R^{49} , R^{51} to R^{56} and R^{64} is present, only one of these has one of the significances just mentioned whilst the other(s) has/have any of the significance(s) mentioned earlier;

L is a direct bond or one of the linkers

- L1: $-(CH_2)_pCHR^{61}[X(CH_2)_pCHR^{61}]_o-$;
 L2: $-CO(CH_2)_pCHR^{61}[X(CH_2)_pCHR^{61}]_oCO-$;
 5 L3: $-CONR^{34}(CH_2)_pCHR^{61}[X(CH_2)_pCHR^{61}]_oNR^{34}CO-$;
 L4: $-O(CH_2)_pCHR^{61}[X(CH_2)_pCHR^{61}]_oO-$;
 L5: $-S(CH_2)_pCHR^{61}[X(CH_2)_pCHR^{61}]_oS-$;
 L6: $-NR^{34}(CH_2)_pCHR^{61}[X(CH_2)_pCHR^{61}]_oNR^{34}-$;
 L7: $-(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}-$;
 10 L8: $-CO(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}CO-$;
 L9: $-CONR^{34}(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}NR^{34}CO-$;
 L10: $-O(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}O-$;
 L11: $-S(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}S-$;
 L12: $-NR^{34}(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}NR^{34}-$;
 15 L13: $-CO(CH_2)_pCHR^{61}[X(CH_2)_pCHR^{61}]_oNR^{34}-$;
 L14: $-CO(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}NR^{34}-$;
 L15: $-NR^{34}(CH_2)_pCHR^{61}[X(CH_2)_pCHR^{61}]_oCO-$; and
 L16: $-NR^{34}(CH_2)_oCHR^{61}Y(CH_2)_oCHR^{61}CO-$;
 m, o, p, q, r and s being as defined above; X being O; S; NR^{34} ; $-NR^{32}CONR^{34}-$; or $-OCOO-$;
 20 and Y being $-C_6R^{67}R^{68}R^{69}R^{70}-$;
 R^{67} being H; Cl; Br; F; NO_2 ; $-NR^{34}COR^{57}$; lower alkyl; or lower alkenyl;
 R^{68} being H; Cl; Br; F; NO_2 ; $-NR^{34}COR^{57}$; lower; or lower alkenyl;
 R^{69} being H; Cl; Br; F; NO_2 ; $-NR^{34}COR^{57}$; lower alkyl; or lower alkenyl; and
 R^{70} being H; Cl; Br; F; NO_2 ; $-NR^{34}COR^{57}$; lower alkyl; or lower alkenyl;
 25 with the proviso that at least two of R^{67} , R^{68} , R^{69} and R^{70} are H; and

with the further proviso that

- $-(CH_2)_m(CHR^{61})_sO-$ can be combined with linker L1, L2, L3, L7, L8 or L9;
 $-(CH_2)_o(CHR^{61})_sO-$ can be combined with linker L1, L2, L3, L7, L8 or L9;
 30 $-(CH_2)_p(CHR^{61})_sO-$ can be combined with linker L1, L2, L3, L7, L8 or L9;
 $-(CH_2)_q(CHR^{61})_sO-$ can be combined with linker L1, L2, L3, L7, L8 or L9;
 $-(CHR^{61})_sO-$ can be combined with linker L1, L2, L3, L7, L8 or L9;
 $-(CH_2)_m(CHR^{61})_sS-$ can be combined with linker L1, L2, L3, L7, L8 or L9; or can form a
 disulfide bond with $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sS-$;
 35 $-(CH_2)_q(CHR^{61})_sS-$; or $-(CHR^{61})_sS-$;

- $-(CH_2)_o(CHR^{61})_sS-$ can be combined with linker L1, L2, L3, L7, L8 or L9; or can form a disulfide bond with $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_q(CHR^{61})_sS-$; or $-(CHR^{61})_sS-$;
- 5 $-(CH_2)_p(CHR^{61})_sS-$ can be combined with linker L1, L2, L3, L7, L8 or L9; or can form a disulfide bond with $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_q(CHR^{61})_sS-$; or $-(CHR^{61})_sS-$;
- $-(CH_2)_q(CHR^{61})_sS-$ can be combined with linker L1, L2, L3, L7, L8 or L9; or can form a disulfide bond with $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_q(CHR^{61})_sS-$; or $-(CHR^{61})_sS-$;
- 10 $-(CHR^{61})_sS-$ can be combined with linker L1, L2, L3, L7, L8 or L9; or form a disulfide bond with

 with

 $-(CH_2)_m(CHR^{61})_sS-$; $-(CH_2)_o(CHR^{61})_sS-$; $-(CH_2)_p(CHR^{61})_sS-$; $-(CH_2)_q(CHR^{61})_sS-$; or $-(CHR^{61})_sS-$;
- $-(CH_2)_m(CHR^{61})_sNR^{34}-$ can be combined with linker L1, L2, L3, L7, L8 or L9;
- 15 $-(CH_2)_o(CHR^{61})_sNR^{34}-$ can be combined with linker L1, L2, L3, L7, L8 or L9;

 $-(CH_2)_p(CHR^{61})_sNR^{34}-$ can be combined with linker L1, L2, L3, L7, L8 or L9;

 $-(CH_2)_q(CHR^{61})_sNR^{34}-$ can be combined with linker L1, L2, L3, L7, L8 or L9;

 $-(CHR^{61})_sNR^{34}-$ can be combined with linker L1, L2, L3, L7, L8 or L9;
- $-(CH_2)_o(CHR^{61})_sCO-$ can be combined with linker L4, L5, L6, L10, L11 or L12;
- 20 $-(CH_2)_p(CHR^{61})_sCO-$ can be combined with linker L4, L5, L6, L10, L11 or L12;

 $-(CH_2)_q(CHR^{61})_sCO-$ can be combined with linker L4, L5, L6, L10, L11 or L12;

 $-(CH_2)_r(CHR^{61})_sCO-$ can be combined with linker L4, L5, L6, L10, L11 or L12;

 $-(CHR^{61})_sCO-$ can be combined with linker L4, L5, L6, L10, L11 or L12;
- $-(CH_2)_m(CHR^{61})_sO-$ can be combined with linker L13 or L14 and the resulting combination
- 25 with

 $-(CH_2)_m(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

 $-(CH_2)_o(CHR^{61})_sO-$ can be combined with linker L13 or L14 and the resulting combination

 with

 $-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;
- 30 $-(CH_2)_p(CHR^{61})_sO-$ can be combined with linker L13 or L14 and the resulting combination

 with

 $-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

 $-(CH_2)_q(CHR^{61})_sO-$ can be combined with linker L13 or L14 and the resulting combination

 with
- 35 $-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

 $-(CHR^{61})_sO-$ can be combined with linker L13 or L14 and the resulting combination with

 $-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_m(CHR^{61})_sS-$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_o(CHR^{61})_sS-$ can be combined with linker L13 or L14 and the resulting combination

5 with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_p(CHR^{61})_sS-$ can be combined with linker L13 or L14 and the resulting combination

with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

10 $-(CH_2)_q(CHR^{61})_sS-$ can be combined with linker L13 or L14 and the resulting combination

with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CHR^{61})_sS-$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

15 $-(CH_2)_m(CHR^{61})_sNR^{34}$ can be combined with linker L13 or L14 and the resulting combination

with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_o(CHR^{61})_sNR^{34}$ can be combined with linker L13 or L14 and the resulting combination

with

20 $-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_p(CHR^{61})_sNR^{34}$ can be combined with linker L13 or L14 and the resulting combination

with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_q(CHR^{61})_sNR^{34}$ can be combined with linker L13 or L14 and the resulting combination

25 with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CHR^{61})_sNR^{34}$ can be combined with linker L13 or L14 and the resulting combination with

$-(CH_2)_o(CHR^{61})_sCO-$; $-(CH_2)_o(CHR^{61})_pCO-$; $-(CH_2)_q(CHR^{61})_sCO-$; or $-(CHR^{61})_sCO-$;

$-(CH_2)_o(CHR^{61})_sCO-$ can be combined with linker L15 or L16 and the resulting combination

30 with

$-(CH_2)_m(CHR^{61})_sX-$; $-(CH_2)_o(CHR^{61})_sX-$; $-(CH_2)_p(CHR^{61})_sX-$; $-(CH_2)_q(CHR^{61})_sX-$; or

$-(CHR^{61})_sX-$;

$-(CH_2)_p(CHR^{61})_sCO-$ can be combined with linker L15 or L16 and the resulting combination

with

35 $-(CH_2)_m(CHR^{61})_sX-$; $-(CH_2)_o(CHR^{61})_sX-$; $-(CH_2)_p(CHR^{61})_sX-$; $-(CH_2)_q(CHR^{61})_sX-$; or

$-(CHR^{61})_sX-$;

$-(CH_2)_q(CHR^{61})_sCO-$ can be combined with linker L15 or L16 and the resulting combination with

$-(CH_2)_m(CHR^{61})_sX-$, $-(CH_2)_o(CHR^{61})_sX-$, $-(CH_2)_p(CHR^{61})_sX-$, $-(CH_2)_q(CHR^{61})_sX-$; or $-(CHR^{61})_sX-$;

5 $-(CH_2)_r(CHR^{61})_sCO-$ can be combined with linker L15 or L16 and the resulting combination with

$-(CH_2)_m(CHR^{61})_sX-$, $-(CH_2)_o(CHR^{61})_sX-$, $-(CH_2)_p(CHR^{61})_sX-$, $-(CH_2)_q(CHR^{61})_sX-$; or $-(CHR^{61})_sX-$;

10 $-(CHR^{61})_sCO-$ can be combined with linker L15 or L16 and the resulting combination with $-(CH_2)_m(CHR^{61})_sX-$; $-(CH_2)_o(CHR^{61})_sX-$; $-(CH_2)_p(CHR^{61})_sX-$; $-(CH_2)_q(CHR^{61})_sX-$; or $-(CHR^{61})_sX-$;

15 Z , Z^1 and Z^2 independently are chains of n α -amino acid residues, n being an integer from 8 to 16, the positions of said amino acid residues in said chains being counted starting from the N-terminal amino acid, whereby these amino acid residues are, depending on their position in the chains, Gly, or Pro, or of formula $-A-CO-$, or of formula $-B-CO-$, or of one of the types

C: $-NR^{20}CH(R^{72})CO-$;

D: $-NR^{20}CH(R^{73})CO-$;

E: $-NR^{20}CH(R^{74})CO-$;

20 F: $-NR^{20}CH(R^{84})CO-$; and

H: $-NR^{20}-CH(CO-)-(CH_2)_{4-7}-CH(CO-)-NR^{20}-$;

$-NR^{20}-CH(CO-)-(CH_2)_pSS(CH_2)_p-CH(CO-)-NR^{20}-$;

$-NR^{20}-CH(CO-)-(-(CH_2)_pNR^{20}CO(CH_2)_p-CH(CO-)-NR^{20}-$; and

$-NR^{20}-CH(CO-)-(-(CH_2)_pNR^{20}CONR^{20}(CH_2)_p-CH(CO-)-NR^{20}-$;

25 R^{71} is H; lower alkyl; lower alkenyl; $-(CH_2)_p(CHR^{61})_sOR^{75}$; $-(CH_2)_p(CHR^{61})_sSR^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{33}R^{34}$; $-(CH_2)_p(CHR^{61})_sOCONR^{33}R^{75}$; $-(CH_2)_p(CHR^{61})_sNR^{20}CONR^{33}R^{82}$; $-(CH_2)_o(CHR^{61})_sCOOR^{75}$; $-(CH_2)_pCONR^{58}R^{59}$; $-(CH_2)_pPO(OR^{62})_2$; $-(CH_2)_pSO_2R^{62}$; or $-(CH_2)_o-C_6R^{67}R^{68}R^{69}R^{70}R^{76}$;

R^{72} is H; lower alkyl; lower alkenyl; $-(CH_2)_p(CHR^{61})_sOR^{85}$; or $-(CH_2)_p(CHR^{61})_sSR^{85}$;

30 R^{73} is $-(CH_2)_oR^{77}$; $-(CH_2)_rO(CH_2)_oR^{77}$; $-(CH_2)_rS(CH_2)_oR^{77}$; or $-(CH_2)_rNR^{20}(CH_2)_oR^{77}$;

R^{74} is $-(CH_2)_pNR^{78}R^{79}$; $-(CH_2)_pNR^{77}R^{80}$; $-(CH_2)_pC(=NR^{80})NR^{78}R^{79}$; -

$(CH_2)_pC(=NOR^{50})NR^{78}R^{79}$;

$-(CH_2)_pC(=NNR^{78}R^{79})NR^{78}R^{79}$; $-(CH_2)_pNR^{80}C(=NR^{80})NR^{78}R^{79}$;

$-(CH_2)_pN=C(NR^{78}R^{80})NR^{79}R^{80}$; $-(CH_2)_pC_6H_4NR^{78}R^{79}$; $-(CH_2)_pC_6H_4NR^{77}R^{80}$;

35 $-(CH_2)_pC_6H_4C(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_pC_6H_4C(=NOR^{50})NR^{78}R^{79}$;

$-(CH_2)_pC_6H_4C(=NNR^{78}R^{79})NR^{78}R^{79}$; $-(CH_2)_pC_6H_4NR^{80}C(=NR^{80})NR^{78}R^{79}$;

$-(CH_2)_pC_6H_4N=C(NR^{78}R^{80})NR^{79}R^{80}$; $-(CH_2)_rO(CH_2)_mNR^{78}R^{79}$; $-(CH_2)_rO(CH_2)_mNR^{77}R^{80}$;

- $-(CH_2)_rO(CH_2)_pC(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_rO(CH_2)_pC(=NOR^{50})NR^{78}R^{79}$;
 $-(CH_2)_rO(CH_2)_pC(=NNR^{78}R^{79})NR^{78}R^{79}$; $-(CH_2)_rO(CH_2)_mNR^{80}C(=NR^{80})NR^{78}R^{79}$;
 $-(CH_2)_rO(CH_2)_mN=C(NR^{78}R^{80})NR^{79}R^{80}$; $-(CH_2)_rO(CH_2)_pC_6H_4CNR^{78}R^{79}$;
 $-(CH_2)_rO(CH_2)_pC_6H_4C(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_rO(CH_2)_pC_6H_4C(=NOR^{50})NR^{78}R^{79}$;
 5 $-(CH_2)_rO(CH_2)_pC_6H_4C(=NNR^{78}R^{79})NR^{78}R^{79}$;
 $-(CH_2)_rO(CH_2)_pC_6H_4NR^{80}C(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_rS(CH_2)_mNR^{78}R^{79}$;
 $-(CH_2)_rS(CH_2)_mNR^{77}R^{80}$; $-(CH_2)_rS(CH_2)_pC(=NR^{80})NR^{78}R^{79}$;
 $-(CH_2)_rS(CH_2)_pC(=NOR^{50})NR^{78}R^{79}$; $-(CH_2)_rS(CH_2)_pC(=NNR^{78}R^{79})NR^{78}R^{79}$;
 $-(CH_2)_rS(CH_2)_mNR^{80}C(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_rS(CH_2)_mN=C(NR^{78}R^{80})NR^{79}R^{80}$;
 10 $-(CH_2)_rS(CH_2)_pC_6H_4CNR^{78}R^{79}$; $-(CH_2)_rS(CH_2)_pC_6H_4C(=NR^{80})NR^{78}R^{79}$;
 $-(CH_2)_rS(CH_2)_pC_6H_4C(=NOR^{50})NR^{78}R^{79}$; $-(CH_2)_rS(CH_2)_pC_6H_4C(=NNR^{78}R^{79})NR^{78}R^{79}$;
 $-(CH_2)_rS(CH_2)_pC_6H_4NR^{80}C(=NR^{80})NR^{78}R^{79}$; $-(CH_2)_pNR^{80}COR^{64}$; $-(CH_2)_pNR^{80}COR^{77}$;
 $-(CH_2)_pNR^{80}CONR^{78}R^{79}$; or $-(CH_2)_pC_6H_4NR^{80}CONR^{78}R^{79}$;

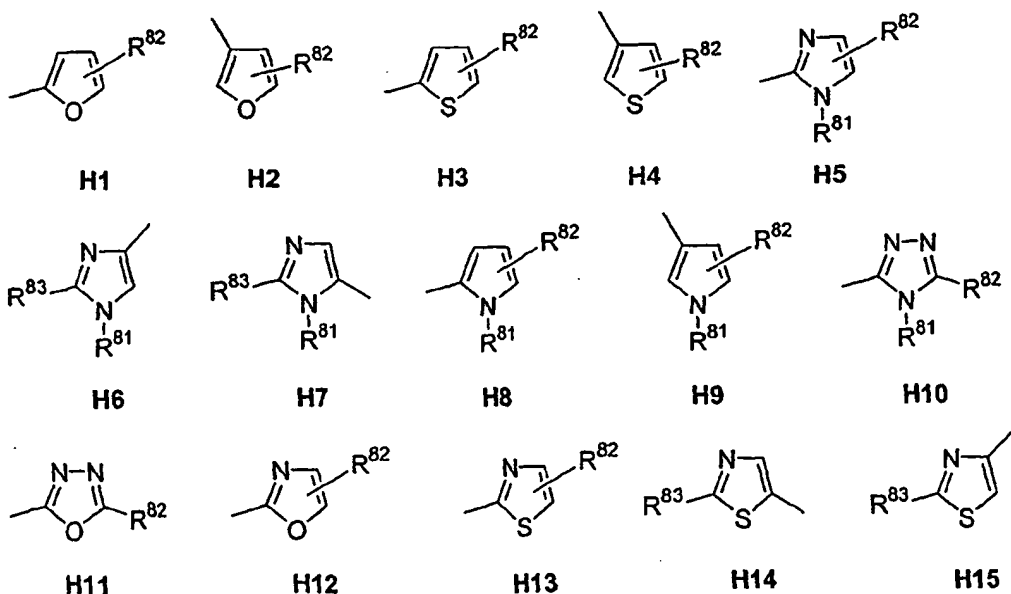
R^{75} is lower alkyl; lower alkenyl; or aryl-lower alkyl;

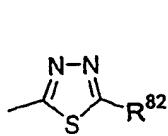
- 15 R^{33} and R^{75} taken together can form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$;

R^{75} and R^{82} taken together can form: $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$;

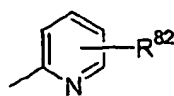
- R^{76} is H; lower alkyl; lower alkenyl; aryl-lower alkyl; $-(CH_2)_6OR^{72}$; $-(CH_2)_6SR^{72}$;
 20 $-(CH_2)_6NR^{33}R^{34}$; $-(CH_2)_6OCONR^{33}R^{75}$; $-(CH_2)_6NR^{20}CONR^{33}R^{82}$;
 $-(CH_2)_6COOR^{75}$; $-(CH_2)_6CONR^{58}R^{59}$; $-(CH_2)_6PO(OR^{60})_2$; $-(CH_2)_6SO_2R^{62}$; or
 $-(CH_2)_6COR^{64}$;

R^{77} is $-C_6R^{67}R^{68}R^{69}R^{70}R^{76}$; or a heteroaryl group of one of the formulae

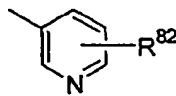




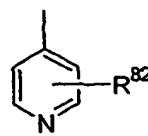
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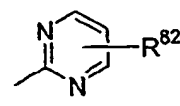
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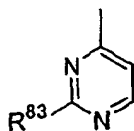
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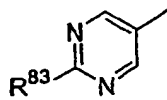
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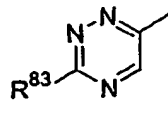
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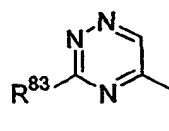
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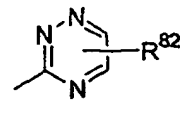
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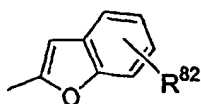
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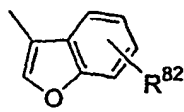
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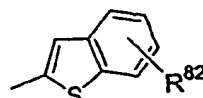
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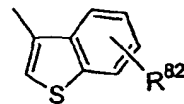
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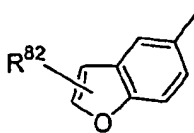
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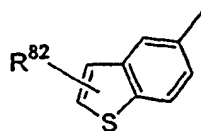
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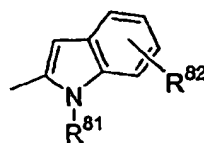
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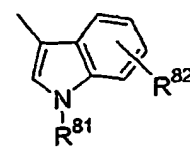
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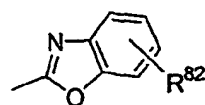
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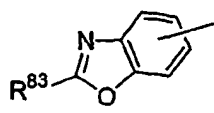
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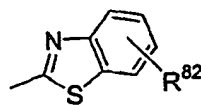
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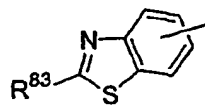
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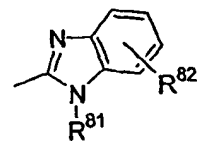
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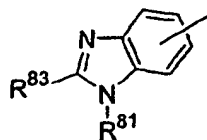
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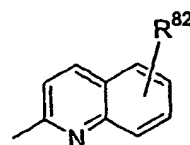
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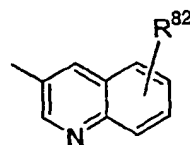
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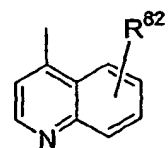
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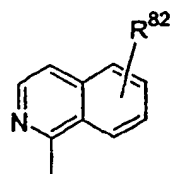
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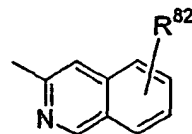
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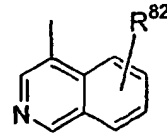
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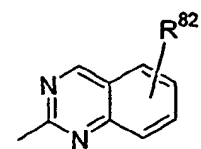
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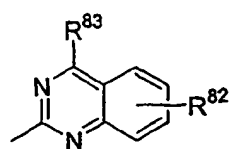
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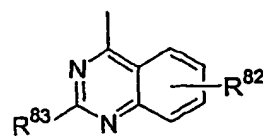
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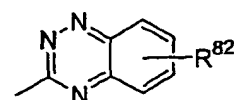
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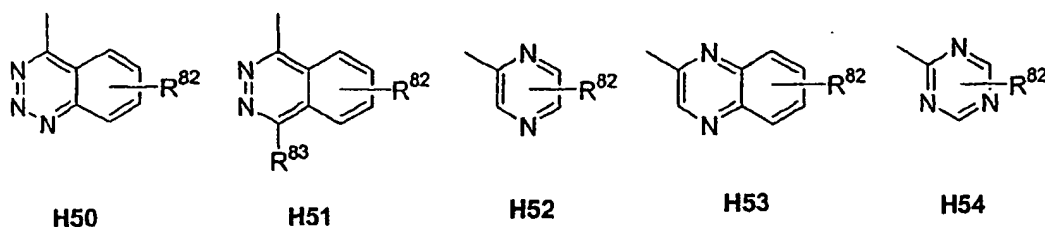
H47



H48



H49



R^{78} is H; lower alkyl; aryl; or aryl-lower alkyl;

R^{78} and R^{82} taken together can form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$;

5 R^{79} is H; lower alkyl; aryl; or aryl-lower alkyl; or

R^{78} and R^{79} , taken together, can be $-(CH_2)_{2-7}-$; $-(CH_2)_2O(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$;

R^{80} is H; or lower alkyl;

R^{81} is H; lower alkyl; or aryl-lower alkyl;

R^{82} is H; lower alkyl; aryl; heteroaryl; or aryl-lower alkyl;

10 R^{83} and R^{82} taken together can form: $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$;

R^{83} is H; lower alkyl; aryl; or $-NR^{78}R^{79}$;

R^{84} is $-(CH_2)_m(CHR^{61})_sOH$; $-(CH_2)_pCONR^{78}R^{79}$; $-(CH_2)_pNR^{80}CONR^{78}R^{79}$; $-(CH_2)_pC_6H_4CONR^{78}R^{79}$; or

15 $-(CH_2)_pC_6H_4NR^{80}CONR^{78}R^{79}$;

R^{85} is lower alkyl; or lower alkenyl;

with the proviso that in said chain(s) of n α -amino acid residues Z , Z^1 and Z^2

- if n is 8, the amino acid residues in positions 1 to 8 are:

20 - P1: of type C or or of type D or of type E or of type F, or the residue is Pro;

- P2: of type E or of type D or of type F;

- P3: of type E or of type C, or the residue is Pro;

- P4: of type E or of formula $-A-CO-$;

25 - P5: of type E or of formula $-B-CO-$, or the residue is Gly;

- P6: of type D, or the residue is Pro;

- P7: of type or of type C or of type D or of type E; and

- P8: of type C or of type D or of type E or of type F, or the residue is Pro; or

30 P2 and P7, taken together, can form a group of type H; and at P4 and P5 also D-isomers being possible;

- if n is 9, the amino acid residues in positions 1 to 9 are:
 - P1: of type C or of type D or of type E or of type F, or the residue is Pro;
 - 5 - P2: of type E or of type D or of type F;
 - P3: of type C or of type D or of type E, or the residue is Pro;
 - P4: of type E or of type D, or the residue is Pro;
 - P5: of type E, or the residue is Gly or Pro;
 - P6: of type D or of type E, or the residue is Gly or Pro;
 - 10 - P7: of type E or of type D or of type C, or the residue is Pro;
 - P8: of type E or of type D; and
 - P9: of type C or of type D or of type E or of type F, or the residue is Pro; or
 - P2 and P8, taken together, can form a group of type H; and at P4, P5 and P6 also D-isomers being possible;
 - 15
- if n is 10, the amino acid residues in positions 1 to 10 are:
 - P1: of type C or of type D or of type E or of type F, or the residue is Pro;
 - 20 - P2: of type E or of type D, or the residue is Pro;
 - P3: of type C or of type E;
 - P4: of type E or of type D or of type F, or the residue is Pro;
 - P5: of type E or of type F or of formula -A-CO-, or the residue is Gly;
 - P6: of type E or of formula -B-CO-, or the residue is Gly;
 - 25 - P7: of type D or of type E, or the residue is Gly or Pro;
 - P8: of type D or of type E;
 - P9: of type E or of type D or of type C, or the residue is Pro; and
 - P10: of type C or of type D or of type E or of type F; or
 - P3 and P8, taken together, can form a group of type H; and at P5 and P6 also D-isomers being possible;
 - 30
- if n is 11, the amino acid residues in positions 1 to 11 are:
 - P1: of type C or of type D or of type E or of type F, or the residue is Pro;
 - 35 - P2: of type E or of type C or of type D;
 - P3: of type D or of type E, or the residue is Pro;
 - P4: of type E or of type C or of type F;

- P5: of type E or of type F, or the residue is Gly or Pro;
- P6: of type E or of type F, or the residue is Gly or Pro;
- P7: of type E or of type F, or the residue is Gly or P ro;
- P8: of type D or of type E or of type F;
- 5 - P9: of type D or of type E, or the residue is Pro;
- P10: of type E or of type C or of type D; and
- P11: of type C or of type D or of type E or of type F, or the residue is Pro; or
- P4 and P8 and/or P2 and P10, taken together, can form a group of type H; and
- 10 at P5, P6 and P7 also D-isomers being possible;

- if n is 12, the amino acid residues in positions 1 to 12 are:

- P1: of type C or of type D or of type E or of type F, or the residue is Pro;
- 15 - P2: of type E or of type D;
- P3: of type C or of type D, or the residue is Pro;
- P4: of type E or of type F or of type D;
- P5: of type E or of type D or of type C, or the residue is Gly or Pro;
- P6: of type E or of type F or of formula -A-CO-, or the residue is Gly;
- 20 - P7: of type E or of type F or of formula -B-CO-;
- P8: of type D or of type C, or the residue is Pro;
- P9: of type E or of type D or of type F;
- P10: of type D or of type C, or the residue is Pro;
- P11: of type E or of type D; and
- 25 - P12: of type C or of type D or of type E or of type F, or the residue is Pro; or
- P4 and P9 and/or P2 and P11, taken together, can form a group of type H; and at P6 and P7 also D-isomers being possible;

30 - if n is 13, the amino acid residues in positions 1 to 13 are:

- P1: of type C or of type D or of type E or of type F, or the residue is Pro;
- P2: of type E or of type F or of type D;
- P3: of type C or of type D or of type E, or the residue is Pro;
- P4: of type E or of type C or of type F;
- 35 P5: of type E or of type D, or the residue is Gly or Pro;
- P6: of type E or of type F, or the residue is Gly or Pro;
- P7: of type E or of type F, or the residue is Pro;

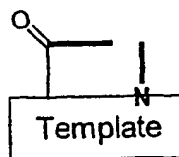
- P8: of type D or of type E or of type F, or the residue is Pro; .
 P9: of type D or of type E, or the residue is Pro;
 P10: of type E or of type C or of type F;
 P11: of type C or of type E, or the residue is Pro;
 5 P12: of type E or of type D or of type C; and
 P13: of type C or of type D or of type E or of type F, or the residue is Pro; or
 P4 and P10 and/or P2 and P12, taken together, can form a group of type H;
 and at P6, P7 and P8 also D-isomers being possible;
- 10 - if n is 14, the amino acid residues in positions 1 to 14 are:
- P1: of type C or of type D or of type E or of type F, or the residue is Pro;
 - P2: of type E or of type C or of type D, or the residue is Pro;
 - P3: of type C or of type D or of type E;
 - 15 - P4: of type D or of type C or of type E, or the residue is Pro;
 - P5: of type E or of type D;
 - P6: of type E or of type F, or the residue is Gly or Pro;
 - P7: of type E or of type F or of formula -A-CO-, or the residue is Gly;
 - P8: of type E or of type F or of formula -B-CO-, or the residue is Gly;
 - 20 - P9: of type D or of type E, or the residue is Pro;
 - P10: of type C or of type D or of type E;
 - P11: of type E or of type D or of type F, or the residue is Pro;
 - P12: of type D or of type E;
 - P13: of type E or of type C or of type D, or the residue is Pro; and
 - 25 - P14: of type C or of type D or of type E or of type F, or the residue is Pro; or
 - P5 and P10 and/or P3 and P12, taken together, can form a group of type H;
 and at P7 and P8 also D-isomers being possible;
- 30 - if n is 15, the amino acid residues in positions 1 to 15 are:
- P1: of type C or of type D or of type E or of type F, or the residue is Pro;
 - P2: of type E or of type F or of type D;
 - P3: of type C or of type D or of type E, or the residue is Pro;
 - 35 P4: of type E or of type D or of type F;
 - P5: of type C or of type D or of type E, or the residue is Pro;
 - P6: of type E or of type D or of type F;

- P7: of type C or of type E, or the residue is Pro;
 P8: of type E or of type F, or the residue is Gly or Pro;
 P9: of type E or of type F, or the residue is Gly or Pro;
 P10: of type E or of type D;
 5 P11: of type C or of type D or of type E, or the residue is Pro;
 P12: of type E or of type C or of type F;
 P13: of type D or of type E, or the residue is Pro;
 P14: of type E or of type C or of type D; and
 P15: of type C or of type D or of type E or of type F, or the residue is
 10 Pro; or
 P6 and P10 and/or P4 and P12 and/or P2 and P14, taken together, can form a
 group of type H; and at P7, P8 and P9 also D-isomers being possible; and

- if n is 16, the amino acid residues in positions 1 to 16 are:
- 15 - P1: of type D, or of type E or of type C or of type F, or the residue is
 Pro;
 - P2: of type E or of type F or of type D;
 - P3: of type C or of type D or of type E, or the residue is Pro;
 - P4: of type E or of type D or of type F;
 20 - P5: of type D or of type C or of type E, or the residue is Pro;
 - P6: of type E or of type D;
 - P7: of type E or of type F, or the residue is Gly or Pro;
 - P8: of type E or of type F or of formula -A-CO-, or the residue is Gly;
 - P9: of type E or of formula -B-CO-, or the residue is Gly;
 25 - P10: of type D or of type E, or the residue is Pro;
 - P11: of type E or of type C or of type D;
 - P12: of type D or of type C or of type E, or the residue is Pro;
 - P13: of type E or of type C or of type F;
 - P14: of type C or of type D or of type E, or the residue is Pro;
 30 - P15: of type E or of type C or of type D; and
 - P16: of type C or of type D or of type E or of type F, or the residue is
 Pro; or
 - P6 and P11 and/or P4 and P13 and/or P2 and P15, taken together, can form a
 group of type H; and at P8 and P9 also D-isomers being possible;

35

and pharmaceutically acceptable salts thereof.



2. Compounds according to claim 1 wherein

is other than a group of formula (a2);

5 R^2 to R^{19} , R^{21} to R^{29} , R^{31} , R^{35} to R^{38} , R^{41} to R^{45} , R^{51} to R^{54} and R^{76} are other than

$-(CH_2)_m(CHR^{61})_sOCONR^{33}R^{75}$ or $-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{33}R^{82}$;

R^{33} , R^{55} , R^{56} , R^{61} and R^{64} are other than $-(CH_2)_m(CHR^{61})_sOCONR^{75}R^{82}$ or

$-(CH_2)_m(CHR^{61})_sNR^{20}CONR^{78}R^{82}$;

R^{33} and R^{34} , or R^{34} and R^{63} are other than, taken together, $-CH_2-$; $-(CH_2)_2O(CH_2)_2-$,

10 $-(CH_2)_2S(CH_2)_2-$ or $-(CH_2)_2NR^{57}(CH_2)_2-$;

R^{57} in $-(CH_2)_2NR^{57}(CH_2)_2-$ or $-(CH_2)_pNR^{57}(CH_2)_p-$ is other than lower alkenyl or heteroaryl-lower alkyl;

R^{71} is H, lower alkyl, lower alkenyl, $-(CH_2)_p(CHR^{61})_sOR^{75}$, $-(CH_2)_p(CHR^{61})_sSR^{75}$, $-(CH_2)_pNR^xR^y$,

15 $-(CH_2)_p(CHR^{61})_sCOOR^{75}$, $-(CH_2)_pCONR^xR^y$, $-(CH_2)_pPO(OR^{62})_2$, $-(CH_2)_pSO_2R^{62}$, or

$-(CH_2)_p-C_6R^{67}R^{68}R^{69}R^{70}R^{76}$;

R^{74} is other than $-(CH_2)_pNR^{77}R^{80}$, $-(CH_2)_pC_6H_4NR^{77}R^{80}$,

$-(CH_2)_pO(CH_2)_mNR^{77}R^{80}$, $-(CH_2)_pS(CH_2)_mNR^{77}R^{80}$, $-(CH_2)_pN=C(NR^{78}R^{80})NR^{79}R^{80}$,

$-(CH_2)_pC_6H_4N=C(NR^{78}R^{80})NR^{79}R^{80}$, $-(CH_2)_pO(CH_2)_mN=C(NR^{78}R^{80})NR^{79}R^{80}$,

20 $-(CH_2)_pS(CH_2)_mN=C(NR^{78}R^{80})NR^{79}R^{80}$, $-(CH_2)_pNR^{80}COR^{64}$, or $-(CH_2)_pNR^{80}COR^{77}$;

is other than H52, H53 and H54;

in Z, Z^1 or Z^2

- if n is 8, the amino acid residues in positions 1, 7 and 8 are:

- P1: of type C or of type D or of type E, or the residue is Pro;

25 - P7: of type C or of type D; and

- P8: of type C or of type D or of type E, or the residue is Pro;

- if n is 9, the amino acid residues in positions 1 and 9 are:

- P1: of type C or of type D or of type E, or the residue is Pro; and

- P9: of type C or of type D or of type E, or the residue is Pro;

30 - if n is 10, the amino acid residues in positions 1 and 10 are:

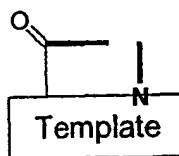
- P1: of type C or of type D or of type E, or the residue is Pro; and

- P10: of type C or of type D or of type E;

- if n is 11, the amino acid residues in positions 1 and 11 are:

- P1: of type C or of type D or of type E, or the residue is Pro; and
- P11: of type C or of type D or of type E, or the residue is Pro;
- if n is 12, the amino acid residues in positions 1, 5 and 12 are:
 - P1: of type C or of type D or of type E, or the residue is Pro;
 - P5: of type E or of type D, or the residue is Gly or Pro; and
 - P12: of type C or of type D or of type E, or the residue is Pro;
- if n is 13, the amino acid residues in positions 1 and 13 are:
 - P1: of type C or of type D or of type E, or the residue is Pro; and
 - P13: of type C or of type D or of type E, or the residue is Pro;
- if n is 14, the amino acid residues in positions 1 and 14 are:
 - P1: of type C or of type D or of type E, or the residue is Pro; and
 - P14: of type C or of type D or of type E, or the residue is Pro;
- if n is 15, the amino acid residues in positions 1 and 15 are:
 - P1: of type C or of type D or of type E, or the residue is Pro; and
 - P15: of type C or of type D or of type E, or the residue is Pro;
- if n is 16, the amino acid residues in positions 1 and 16 are:
 - P1: of type D or of type E or of type C, or the residue is Pro; and
 - P16: of type C or of type D or of type E, or the residue is Pro.

- 20 3. Compounds according to claim 1 or 2 wherein



is a group of formula (a1) or (a2).

4. Compounds according to claim 3 wherein A is a group of one of the formulae A1 to
- 25 A69;
- R^1 is hydrogen or lower alkyl;
- R^2 is H; lower alkyl; lower alkenyl; $-(CH_2)_mOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl);
- $-(CH_2)_mSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_mNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}$;
- 30 $-(CH_2)_2O(CH_2)_2$;
- $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl);
- $-(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} is H; lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are

- $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl);
 $-(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2-6}$;
5 $-(CH_2)_2O(CH_2)_2$;
 $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl);
 $-(CH_2)_6N(R^{20})COR^{64}$ (where: R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl);
 $(CH_2)_6COOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_6CONR^{58}R^{59}$ (where R^{58} is lower alkyl; or lower alkenyl; and R^{59} is H; or lower alkyl; or R^{58} and R^{59} taken together are
10 $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or
 $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_6PO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_6SO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or
 $-(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy);
 R^3 is H; lower alkyl; lower alkenyl; $-(CH_2)_mOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl);
15 $-(CH_2)_mSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_mNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are
 $-(CH_2)_{2-6}$;
 $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl);
 $-(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or
20 R^{33} and R^{75} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or
 $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2-6}$;
 $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl);
25 $-(CH_2)_6N(R^{20})COR^{64}$ (where: R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl);
 $-(CH_2)_6COOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_6CONR^{58}R^{59}$ (where R^{58} is lower alkyl; or lower alkenyl; and R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are
 $-(CH_2)_{2-6}$;
 $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl);
30 $-(CH_2)_6PO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_6SO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
 R^4 is H; lower alkyl; lower alkenyl; $-(CH_2)_mOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl);
 $-(CH_2)_mSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_mNR^{33}R^{34}$ (where R^{33} is
35 lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are
 $-(CH_2)_{2-6}$;
 $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl);

- $-(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_mN(R^{20})COR^{64}$ (where: R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl); $-(CH_2)_oCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} is lower alkyl; or lower alkenyl; and R^{59} is H; or lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2-6}$;
- 10 $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).
- 15 R^5 is lower alkyl; lower alkenyl; $-(CH_2)_oOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl); $-(CH_2)_oSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $(CH_2)_oNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); -
- 20 $(CH_2)_oOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$;
- 25 $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_oN(R^{20})COR^{64}$ (where: R^{20} is H; or lower alkyl; R^{64} is alkyl; alkenyl; aryl; aryl-lower alkyl; or heteroaryl-lower alkyl); $-(CH_2)_oCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} is lower alkyl; or lower alkenyl; and R^{59} is H; or lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$;
- 30 or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy):
- 35 R^6 is H; lower alkyl; lower alkenyl; $-(CH_2)_oOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl); $-(CH_2)_oSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_oNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}$;

- $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl);
 $-(CH_2)_6OCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are
- 5 $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_6NR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are
 $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl);
- 10 $-(CH_2)_6N(R^{20})COR^{64}$ (where R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl);
 $-(CH_2)_6COOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_6CONR^{58}R^{59}$ (where R^{58} is lower alkyl; or lower alkenyl; and R^{59} is H; or lower alkyl; or R^{58} and R^{59} taken together are
 $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or
 $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_6PO(OR^{60})_2$ (where R^{60} is lower
- 15 alkyl; or lower alkenyl); $-(CH_2)_6SO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or
 $-(CH_2)_6C_6H_4R^8$ (where R^8 is H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy);
 R^7 is lower alkyl; lower alkenyl; $-(CH_2)_qOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl);
 $-(CH_2)_qSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_qNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}-$;
- 20 $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); -
 $(CH_2)_qOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are
 $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl; or
- 25 lower alkyl); $-(CH_2)_qNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2-6}-$;
 $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl);
 $-(CH_2)_qN(R^{20})COR^{64}$ (where: R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl);
 $-(CH_2)_rCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_qCONR^{58}R^{59}$ (where R^{58}
- 30 is lower alkyl; or lower alkenyl; and R^{59} is H; or lower alkyl; or R^{58} and R^{59} taken together are
 $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or
 $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_rPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_rSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or
 $-(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy);
- 35 R^8 is H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; $-(CH_2)_6OR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl); $-(CH_2)_6SR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_6NR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken

- together are $-(CH_2)_{2-6}$;
- $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl);
- $-(CH_2)_6OCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or
- R^{33} and R^{75} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or
- 5 $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_6NR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2-6}$;
- $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl);
- $-(CH_2)_6N(R^{20})COR^{64}$ (where R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl);
- 10 $-(CH_2)_6COOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_6CONR^{58}R^{59}$ (where R^{58} is lower alkyl; or lower alkenyl; and R^{59} is H; or lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2-6}$;
- $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl);
- $-(CH_2)_6PO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_6SO_2R^{62}$ (where R^{62} is
- 15 lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy);
- R^9 is lower alkyl; lower alkenyl; $-(CH_2)_6OR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl);
- $-(CH_2)_6SR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_6NR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}$;
- 20 $-(CH_2)_2O(CH_2)_2$;
- $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl);
- $-(CH_2)_6OCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or
- R^{33} and R^{75} taken together are
- $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or
- 25 lower alkyl); $-(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$;
- $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl);
- $-(CH_2)_6N(R^{20})COR^{64}$ (where R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl);
- 30 $-(CH_2)_6COOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_6CONR^{58}R^{59}$ (where R^{58} is lower alkyl; or lower alkenyl; and R^{59} is H; or lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or
- $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_6PO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_6SO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or
- 35 $-(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy);

- R^{10} is lower alkyl; lower alkenyl; $-(CH_2)_6OR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl);
 $-(CH_2)_6SR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_6NR^{33}R^{34}$ (where R^{33} is lower
 alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}$;
 $-(CH_2)_2O(CH_2)_2$;
 5 $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl);
 $-(CH_2)_6OCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or
 R^{33} and R^{75} taken together are
 $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} : H is or
 lower alkyl); $-(CH_2)_6NR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower lower alkyl; R^{33} is H; or
 10 lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are
 $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$;
 $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl);
 $-(CH_2)_6N(R^{20})COR^{64}$ (where R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl);
 $-(CH_2)_6COOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_6CONR^{58}R^{59}$ (where R^{58}
 15 is lower alkyl; or lower alkenyl; and R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are
 $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or
 $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_6PO(OR^{60})_2$ (where R^{60} is lower
 alkyl; or lower alkenyl); $-(CH_2)_6SO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or
 $-(CH_2)_6C_6H_4R^8$ (where R^8 is H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy);
 20 R^{11} is H; lower alkyl; lower alkenyl; $-(CH_2)_mOR^{55}$ (where R^{55} is lower alkyl; or lower
 alkenyl);
 $-(CH_2)_mSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_mNR^{33}R^{34}$ (where R^{33} is
 lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are
 $-(CH_2)_{2-6}$;
 25 $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl);
 $-(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or
 R^{33} and R^{75} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or
 $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20} is
 H; or lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33}
 30 and R^{82} taken together are $-(CH_2)_{2-6}$;
 $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl);
 $-(CH_2)_mN(R^{20})COR^{64}$ (where R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl);
 $-(CH_2)_6COOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_6CONR^{58}R^{59}$ (where R^{58}
 is lower alkyl; or lower alkenyl; and R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are
 35 $-(CH_2)_{2-6}$;
 $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl);
 $-(CH_2)_6PO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_6SO_2R^{62}$ (where R^{62} is

- lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy);
- R^{12} is H; lower alkyl; lower alkenyl; $-(CH_2)_mOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl);
- 5 $-(CH_2)_mSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_mNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}$;
- $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl);
- $-(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or
- 10 R^{33} and R^{75} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2-6}$;
- $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl);
- 15 $-(CH_2)_mN(R^{20})COR^{64}$ (where: R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl);
- $-(CH_2)_rCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_rCONR^{58}R^{59}$ (where R^{58} is lower alkyl; or lower alkenyl; and R^{59} is H; or lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2-6}$;
- $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl);
- 20 $-(CH_2)_rPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy):
- R^{13} is lower alkyl; lower alkenyl; $-(CH_2)_qOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl);
- $-(CH_2)_qSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_qNR^{33}R^{34}$ (where R^{33} is lower
- 25 alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}$;
- $-(CH_2)_2O(CH_2)_2$;
- $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl);
- $-(CH_2)_qOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are
- 30 $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_qNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$;
- $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl);
- 35 $-(CH_2)_qN(R^{20})COR^{64}$ (where: R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl);
- $-(CH_2)_rCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_rCONR^{58}R^{59}$ (where R^{58} is lower alkyl; or lower alkenyl; and R^{59} is H; or lower alkyl; or R^{58} and R^{59} taken together are

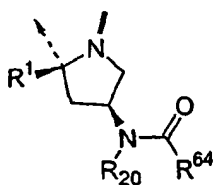
- $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl; $-(CH_2)_2PO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_2SO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy);
- 5 R^{14} is H; lower alkyl; lower alkenyl; $-(CH_2)_mOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl);
 $-(CH_2)_mSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_mNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}-$);
- 10 $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl;
 $-(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl is R^{82} ; H; or lower alkyl; or
- 15 R^{33} and R^{82} taken together are $-(CH_2)_{2-6}-$;
 $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl);
 $-(CH_2)_mN(R^{20})COR^{64}$ (where: R^{20} is H; lower alkyl; R^{64} is lower alkyl; or lower alkenyl);
 $-(CH_2)_oCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} is lower alkyl; or lower alkenyl; and R^{59} is H; or lower alkyl; or R^{58} and R^{59} taken together are
- 20 $-(CH_2)_{2-6}-$;
 $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl);
 $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy);
- 25 R^{15} is lower alkyl; lower alkenyl; $-(CH_2)_oOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl);
 $-(CH_2)_oSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_oNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}-$;
 $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); -
- 30 $(CH_2)_oOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are
- 35 $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl);
 $-(CH_2)_oN(R^{20})COR^{64}$ (where R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl);

- NR²⁰COlower alkyl (R²⁰=H; or lower alkyl); being particularly favoured; -(CH₂)₆COOR⁵⁷ (where R⁵⁷ is lower alkyl; or lower alkenyl); -(CH₂)₆CONR⁵⁸R⁵⁹ (where R⁵⁸ is lower alkyl, or lower alkenyl; and R⁵⁹ is H; lower alkyl; or R⁵⁸ and R⁵⁹ taken together are -(CH₂)₂₋₆;
- 5 -(CH₂)₂O(CH₂)₂-; -(CH₂)₂S(CH₂)₂-; or -(CH₂)₂NR⁵⁷(CH₂)₂-; where R⁵⁷ is H; or lower alkyl);
- (CH₂)₆PO(OR⁶⁰)₂ (where R⁶⁰ is lower alkyl; or lower alkenyl);
- (CH₂)₆SO₂R⁶² (where R⁶² is lower alkyl; or lower alkenyl); or (CH₂)_qC₆H₄R⁸ (where R⁸ is H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy);
- R¹⁶ is lower alkyl; lower alkenyl; -(CH₂)₆OR⁵⁵ (where R⁵⁵ is lower alkyl; or lower alkenyl);
- (CH₂)₆SR⁵⁶ (where R⁵⁶ is lower alkyl; or lower alkenyl); -(CH₂)₆NR³³R³⁴ (where R³³ is lower
- 10 alkyl; or lower alkenyl; R³⁴ is H; or lower alkyl; or R³³ and R³⁴ taken together are -(CH₂)₂₋₆;
- (CH₂)₂O(CH₂)₂-;
- (CH₂)₂S(CH₂)₂-; or -(CH₂)₂NR⁵⁷(CH₂)₂-; where R⁵⁷ is H; or lower alkyl);
- (CH₂)₆OCONR³³R⁷⁵ (where R³³ is H; or lower alkyl; or lower alkenyl; R⁷⁵ is lower alkyl; or R³³ and R⁷⁵ taken together are
- 15 -(CH₂)₂₋₆; -(CH₂)₂O(CH₂)₂-; -(CH₂)₂S(CH₂)₂-; or -(CH₂)₂NR⁵⁷(CH₂)₂-; where R⁵⁷ is H; or lower alkyl);
- (CH₂)₆NR²⁰CONR³³R⁸² (where R²⁰ is H; or lower lower alkyl; R³³ is H; or lower alkyl; or lower alkenyl; R⁸² is H; or lower alkyl; or R³³ and R⁸² taken together are
- (CH₂)₂₋₆; -(CH₂)₂O(CH₂)₂-;
- (CH₂)₂S(CH₂)₂-; or -(CH₂)₂NR⁵⁷(CH₂)₂-; where R⁵⁷ is H; or lower alkyl);
- 20 -(CH₂)₆N(R²⁰)COR⁶⁴ (where R²⁰ is H; or lower alkyl; R⁶⁴ is lower alkyl; or lower alkenyl);
- (CH₂)₆COOR⁵⁷ (where R⁵⁷ is lower alkyl; or lower alkenyl); -(CH₂)₆CONR⁵⁸R⁵⁹ (where R⁵⁸ is lower alkyl; or lower alkenyl; and R⁵⁹ is H; or lower alkyl; or R⁵⁸ and R⁵⁹ taken together are
- (CH₂)₂₋₆; -(CH₂)₂O(CH₂)₂-; -(CH₂)₂S(CH₂)₂-; or
- (CH₂)₂NR⁵⁷(CH₂)₂-; where R⁵⁷ is H; or lower alkyl); -(CH₂)₆PO(OR⁶⁰)₂ (where R⁶⁰ is lower
- 25 alkyl; or lower alkenyl); -(CH₂)₆SO₂R⁶² (where R⁶² is lower alkyl; or lower alkenyl); or
- (CH₂)_qC₆H₄R⁸ (where R⁸ is H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy); and
- R¹⁷ is lower alkyl; lower alkenyl; -(CH₂)_qOR⁵⁵ (where R⁵⁵ is lower alkyl; or lower alkenyl);
- (CH₂)_qSR⁵⁶ (where R⁵⁶ is lower alkyl; or lower alkenyl); -(CH₂)_qNR³³R³⁴ (where R³³ is lower
- alkyl; or lower alkenyl; R³⁴ is H; or lower alkyl; or R³³ and R³⁴ taken together are -(CH₂)₂₋₆;
- 30 -(CH₂)₂O(CH₂)₂-;
- (CH₂)₂S(CH₂)₂-; or -(CH₂)₂NR⁵⁷(CH₂)₂-; where R⁵⁷ is H; or lower alkyl);
- (CH₂)₆OCONR³³R⁷⁵ (where R³³ is H; or lower alkyl; or lower alkenyl; R⁷⁵ is lower alkyl; or R³³ and R⁷⁵ taken together are
- (CH₂)₂₋₆; -(CH₂)₂O(CH₂)₂-; -(CH₂)₂S(CH₂)₂-; or -(CH₂)₂NR⁵⁷(CH₂)₂-; where R⁵⁷ is H; or
- 35 lower alkyl); -(CH₂)_qNR²⁰CONR³³R⁸² (where R²⁰ is H; or lower alkyl; R³³ is H; or lower
- alkyl; or lower alkenyl; R⁸² is H; or lower alkyl; or R³³ and R⁸² taken together are -(CH₂)₂₋₆;
- (CH₂)₂O(CH₂)₂-; -(CH₂)₂S(CH₂)₂-; or -(CH₂)₂NR⁵⁷(CH₂)₂-; where R⁵⁷ is H; or lower alkyl);

- $-(CH_2)_qN(R^{20})COR^{64}$ (where: R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl);
 $-(CH_2)_rCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_qCONR^{58}R^{59}$ (where R^{58}
 is lower alkyl; or lower alkenyl; and R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are
 $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or
 5 lower alkyl); $-(CH_2)_rPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl);
 $-(CH_2)_rSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 is H;
 F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy).

5. Compounds according to claim 3 or 4 wherein A is a group of one of the formulae A5
 10 (with R^2 being H); A8; A22; A25; A38 (with R^2 being H); A42; and A50.

6. Compounds according to claim 5 wherein A is a group of formula



A8'

- wherein R^{20} is H or lower alkyl; and R^{64} is alkyl; alkenyl; aryl; aryl-lower alkyl; or heteroaryl-
 15 lower alkyl.

7. Compounds according to claim 6 wherein R^{64} is n-hexyl; n-heptyl; 4-(phenyl)benzyl;
 diphenylmethyl, 3-amino-propyl; 5-amino-pentyl; methyl; ethyl; isopropyl; isobutyl; n-
 propyl; cyclohexyl; cyclohexylmethyl; n-butyl; phenyl; benzyl; (3-indolyl)methyl; 2-(3-
 20 indolyl)ethyl; (4-phenyl)phenyl; or n-nonyl.

8. Compounds according to claim 3 wherein A is a group of one of the formulae A70 to
 A104;
 R^{20} is H; or lower alkyl;
 25 R^{18} is lower alkyl;
 R^{19} is lower alkyl; lower alkenyl; $-(CH_2)_pOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl);
 $-(CH_2)_pSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_pNR^{33}R^{34}$ (where R^{33} is lower
 alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}$;
 $-(CH_2)_2O(CH_2)_2$;
 30 $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl);
 $-(CH_2)_pOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or
 R^{33} and R^{75} taken together are

- $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_pNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$;
- 5 $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_pN(R^{20})COR^{64}$ (where: R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl); $-(CH_2)_pCOOR^{57}$ (where R^{57} : lower alkyl; or lower alkenyl); $(CH_2)_pCONR^{58}R^{59}$ (where R^{58} is lower alkyl; or lower alkenyl; and R^{59} is H; or lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or
- 10 lower alkyl); $-(CH_2)_pPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_pSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or $(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy); R^{21} is H; lower alkyl; lower alkenyl; $-(CH_2)_pOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl);
- 15 $-(CH_2)_pSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_pNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_pOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or
- 20 R^{33} and R^{75} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_pNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2-6}$;
- 25 $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_pN(R^{20})COR^{64}$ (where: R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl); $-(CH_2)_pCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_pCONR^{58}R^{59}$ (where R^{58} is lower alkyl; or lower alkenyl; and R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or
- 30 $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_pPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_pSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy); R^{22} is lower alkyl; lower alkenyl; $-(CH_2)_pOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl);
- 35 $-(CH_2)_pSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_pNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}$;

- $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl);
 $-(CH_2)_6OCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are
- 5 $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_6NR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2-6}-$;
 $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl);
 $-(CH_2)_6N(R^{20})COR^{64}$ (where R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl);
- 10 $-(CH_2)_6COOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_6CONR^{58}R^{59}$ (where R^{58} is lower alkyl, or lower alkenyl; and R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2-6}-$;
 $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_6PO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl);
 $-(CH_2)_6SO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 is H;
- 15 F; Cl; CF; lower alkyl; lower alkenyl; or lower alkoxy);
 R^{23} is H; lower alkyl; lower alkenyl; $-(CH_2)_6OR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl);
 $-(CH_2)_6SR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_6NR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}-$;
- 20 $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl);
 $-(CH_2)_6OCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are
- 25 $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_6NR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2-6}-$;
 $-(CH_2)_2O(CH_2)_2-$;
 $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl);
 $-(CH_2)_6N(R^{20})COR^{64}$ (where: R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl);
- 30 $-NR^{20}CO$ lower alkyl ($R^{20}=H$; or lower alkyl) being particularly favoured; $-(CH_2)_6COOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_6CONR^{58}R^{59}$ (where R^{58} is lower alkyl, or lower alkenyl; and R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2-6}-$;
 $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl);
 $-(CH_2)_6PO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl);
- 35 $-(CH_2)_6SO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy);

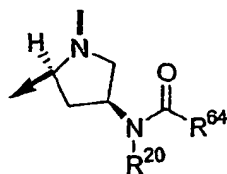
- R^{24} is lower alkyl; lower alkenyl; $-(CH_2)_oOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl);
 $-(CH_2)_oSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_oNR^{33}R^{34}$ (where R^{33} is lower
 alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}$;
 $-(CH_2)_2O(CH_2)_2$;
 5 $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl);
 $-(CH_2)_oCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or
 R^{33} and R^{75} taken together are
 $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or
 lower alkyl); $-(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower lower alkyl; R^{33} is H; or
 10 lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are
 $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$;
 $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); -
 $(CH_2)_oN(R^{20})COR^{64}$ (where: R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl);
 $-NR^{20}CO$ lower alkyl ($R^{20}=H$; or lower alkyl) being particularly favoured; $-(CH_2)_oCOOR^{57}$
 15 (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} is lower alkyl, or
 lower alkenyl; and R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2-6}$; -
 $(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl);
 $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl);
 $-(CH_2)_oSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 is H;
 20 F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy);
 R^{25} is H; lower alkyl; lower alkenyl; $-(CH_2)_mOR^{55}$ (where R^{55} is lower alkyl; or lower
 alkenyl);
 $-(CH_2)_mNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33}
 and R^{34} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or -
 25 $(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} is H; or
 lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are $-(CH_2)_{2-6}$;
 $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or
 $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20} is
 H; or lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33}
 30 and R^{82} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or
 $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_mN(R^{20})COR^{64}$ (where: R^{20} is H;
 or lower alkyl; R^{64} is lower alkyl; or lower alkenyl); $-(CH_2)_oCOOR^{57}$ (where R^{57} is lower
 alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} is lower alkyl; or lower alkenyl; and
 R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$;
 35 $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl);
 $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} is

- lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy);
- R^{26} is H; lower alkyl; lower alkenyl; $-(CH_2)_mOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl);
- 5 $-(CH_2)_mNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or
- 10 $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_mN(R^{20})COR^{64}$ (where: R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl); $-(CH_2)_oCOOR^{57}$ (where R^{57} is lower
- 15 alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} is lower alkyl; or lower alkenyl; and R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy); or, alternatively, R^{25} and R^{26} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{34}(CH_2)_2$;
- 20 R^{27} is H; lower alkyl; lower alkenyl; $-(CH_2)_oOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl);
- 25 $-(CH_2)_oSR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_oNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_oOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or
- 30 R^{33} and R^{75} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_oNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$;
- 35 $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_oN(R^{20})COR^{64}$ (where R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl);

- $-(CH_2)_6COOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_6CONR^{58}R^{59}$ (where R^{58} is lower alkyl, or lower alkenyl; and R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_6PO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_6SO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy); R^{28} is lower alkyl; lower alkenyl; $-(CH_2)_6OR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl); $-(CH_2)_6SR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_6NR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_6OCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_6NR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_6N(R^{20})COR^{64}$ (where: R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl); $-(CH_2)_6COOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_6CONR^{58}R^{59}$ (where R^{58} is lower alkyl, or lower alkenyl; and R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_6PO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_6SO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy); and R^{29} is lower alkyl; lower alkenyl; $-(CH_2)_6OR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl); $-(CH_2)_6SR^{56}$ (where R^{56} is lower alkyl; or lower alkenyl); $-(CH_2)_6NR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_6OCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_6NR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_6N(R^{20})COR^{64}$ (where: R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl);

- NR²⁰CO-lower-alkyl (R²⁰=H; or lower alkyl) being particularly favoured; -(CH₂)₆COOR⁵⁷ (where R⁵⁷ is lower alkyl; or lower alkenyl);
- (CH₂)₆CONR⁵⁸R⁵⁹ (where R⁵⁸ is lower alkyl, or lower alkenyl; and R⁵⁹ is H; lower alkyl; or R⁵⁸ and R⁵⁹ taken together are -(CH₂)₂₋₆-; -(CH₂)₂O(CH₂)₂-; -(CH₂)₂S(CH₂)₂-; or
- 5 -(CH₂)₂NR⁵⁷(CH₂)₂-; where R⁵⁷ is H; or lower alkyl); -(CH₂)₆PO(OR⁶⁰)₂ (where R⁶⁰ is lower alkyl; or lower alkenyl);
- (CH₂)₆SO₂R⁶² (where R⁶² is lower alkyl; or lower alkenyl); or -(CH₂)_qC₆H₄R⁸ (where R⁸ is H; F; Cl; CF₃; lower alkyl; lower alkenyl; or lower alkoxy).
- 10 9. Compounds according to claim 8 wherein R²³, R²⁴ and R²⁹ are -NR²⁰-CO-lower alkyl where R²⁰ is H; or lower alkyl.
10. Compounds according to claim 8 or 9 wherein A is a group of one of the formulae A74 (with R²² being H); a75; A76; A77 (with R²² being H); A78; and A79.
- 15 11. Compounds according to any one of claims 3 to 10 wherein B is a group of formula -NR²⁰CH(R⁷¹)- or an enantiomer of one of the groups A5 (with R² being H); A8; A22; A25; A38 (with R² being H); A42; A47; and A50.
- 20 12. Compounds according to claim 11 wherein B-CO is Ala; Arg; Asn; Cys; Gln; Gly; His; Ile; Leu; Lys; Met; Phe; Pro; Ser; Thr; Trp; Tyr; Val; Cit; Orn; tBuA; Sar; t-BuG; 4AmPhe; 3AmPhe; 2AmPhe; Phe(mC(NH₂)=NH; Phe(pC(NH₂)=NH; Phe(mNHC(NH₂)=NH; Phe(pNHC(NH₂)=NH; Phg; Cha; C₄al; C₅al; Nle; 2-Nal; 1-Nal; 4Cl-Phe; 3Cl-Phe; 2Cl-Phe; 3,4Cl₂Phe; 4F-Phe; 3F-Phe; 2F-Phe; Tic; Thi; Tza; Mso; AcLys; Dpr; A₂Bu; Dbu; Abu; Aha;
- 25 Aib; Y(Bzl); Bip; S(Bzl); T(Bzl); hCha; hCys; hSer; hArg; hPhe; Bpa; Pip; OctG; MePhe; MeNle; MeAla; Melle; MeVal; or MeLeu.

13. Compounds according to claim 11 or 12 wherein B is a group, having (L)-configuration, of formula

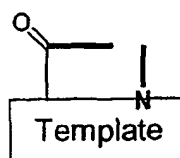


A8''

wherein R²⁰ is H; or lower alkyl; and R⁶⁴ is alkyl; alkenyl; aryl; aryl-lower alkyl; or heteroaryl-lower alkyl.

14. Compounds according to claim 13 wherein R^{64} is n-hexyl; n-heptyl; 4-(phenyl)benzyl; diphenylmethyl; 3-amino-propyl; 5-amino-pentyl; methyl; ethyl; isopropyl; isobutyl; n-propyl; cyclohexyl; cyclohexylmethyl; n-butyl; phenyl; benzyl; (3-indolyl)methyl; 2-(3-indolyl)ethyl; (4-phenyl)phenyl; or n-nonyl.

15. Compounds according to claim 1 or 2 wherein



is a group of formula (b1) or (1);

- 10 R^1 is H; or lower alkyl;

R^{20} is H; or lower alkyl;

R^{30} is H; or methyl;

R^{31} is H; lower alkyl; lower alkenyl; $-(CH_2)_pOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl);

- 15 $-(CH_2)_pNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_pOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or

- 20 $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_pNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_pN(R^{20})COR^{64}$ (where: R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl); $-(CH_2)_oCOOR^{57}$ (where R^{57} is lower

- 25 alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} is lower alkyl, or lower alkenyl; and R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl);

$-(CH_2)_oPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or $-(CH_2)_oC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3 ; lower alkyl;

- 30 lower alkenyl; or lower alkoxy); most preferably $-CH_2CONR^{58}R^{59}$ (where R^{58} is H; or lower alkyl; and R^{59} is lower alkyl; or lower alkenyl);

R^{32} is H; or methyl;

- R^{33} is lower alkyl; lower alkenyl; $-(CH_2)_mOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl);
 $-(CH_2)_mNR^{34}R^{63}$ (where R^{34} is lower alkyl; or lower alkenyl; R^{63} is H; or lower alkyl; or R^{34}
 and R^{63} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or
 $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_mOCONR^{75}R^{82}$ (where R^{75} is
 5 lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{75} and R^{82} taken together are
 $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or
 $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_mNR^{20}CONR^{78}R^{82}$ (where R^{20} is
 H; or lower alkyl; R^{78} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{78}
 and R^{82} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or
 10 $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_mN(R^{20})COR^{64}$ (where: R^{20} is H;
 or lower alkyl; R^{64} is lower alkyl; or lower alkenyl); $-(CH_2)_6COOR^{57}$ (where R^{57} is lower
 alkyl; or lower alkenyl); $-(CH_2)_6CONR^{58}R^{59}$ (where R^{58} is lower alkyl; or lower alkenyl; and
 R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$;
 $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl);
 15 R^{34} is H; or lower alkyl;
 R^{35} is H; lower alkyl; lower alkenyl; $(CH_2)_mOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl);
 $-(CH_2)_mNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33}
 and R^{34} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or
 $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_mOCONR^{33}R^{75}$ (where R^{33} is H;
 20 or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are
 $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or
 $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_mNR^{20}CONR^{33}R^{82}$ (where R^{20} is
 H; or lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33}
 and R^{82} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or
 25 $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_mN(R^{20})COR^{64}$ (where: R^{20} is H;
 or lower alkyl; R^{64} is lower alkyl; or lower alkenyl); $-(CH_2)_6COOR^{57}$ (where R^{57} is lower
 alkyl; or lower alkenyl); $-(CH_2)_6CONR^{58}R^{59}$ (where R^{58} is lower alkyl; or lower alkenyl; and
 R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$;
 $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl);
 30 R^{36} is lower alkyl; lower alkenyl; or aryl-lower alkyl;
 R^{37} is H; lower alkyl; lower alkenyl; $-(CH_2)_pOR^{55}$ (where R^{55} is lower alkyl; or lower
 alkenyl);
 $-(CH_2)_pNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33}
 and R^{34} taken together are $-(CH_2)_{2-6}$; $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or
 35 $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl); $-(CH_2)_pOCONR^{33}R^{75}$ (where R^{33} is H;
 or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are $-(CH_2)_{2-6}$;
 $-(CH_2)_2O(CH_2)_2$; $-(CH_2)_2S(CH_2)_2$; or $-(CH_2)_2NR^{57}(CH_2)_2$; where R^{57} is H; or lower alkyl);
 6;

- $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or
 $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl; $-(CH_2)_pNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or
 5 $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl; $-(CH_2)_pN(R^{20})COR^{64}$ (where: R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl); $-(CH_2)_oCOOR^{57}$ (where R^{57} is lower alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} is lower alkyl, or lower alkenyl; and R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl);
 10 $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3 ; lower alkyl; lower alkenyl; or lower alkoxy); and R^{38} is H; lower alkyl; lower alkenyl; $-(CH_2)_pOR^{55}$ (where R^{55} is lower alkyl; or lower alkenyl);
 15 $-(CH_2)_pNR^{33}R^{34}$ (where R^{33} is lower alkyl; or lower alkenyl; R^{34} is H; or lower alkyl; or R^{33} and R^{34} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_pOCONR^{33}R^{75}$ (where R^{33} is H; or lower alkyl; or lower alkenyl; R^{75} is lower alkyl; or R^{33} and R^{75} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or
 20 $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_pNR^{20}CONR^{33}R^{82}$ (where R^{20} is H; or lower alkyl; R^{33} is H; or lower alkyl; or lower alkenyl; R^{82} is H; or lower alkyl; or R^{33} and R^{82} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or
 $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl); $-(CH_2)_pN(R^{20})COR^{64}$ (where: R^{20} is H; or lower alkyl; R^{64} is lower alkyl; or lower alkenyl); $-(CH_2)_oCOOR^{57}$ (where R^{57} is lower
 25 alkyl; or lower alkenyl); $-(CH_2)_oCONR^{58}R^{59}$ (where R^{58} is lower alkyl, or lower alkenyl; and R^{59} is H; lower alkyl; or R^{58} and R^{59} taken together are $-(CH_2)_{2-6}-$; $-(CH_2)_2O(CH_2)_2-$; $-(CH_2)_2S(CH_2)_2-$; or $-(CH_2)_2NR^{57}(CH_2)_2-$; where R^{57} is H; or lower alkyl);
 $-(CH_2)_oPO(OR^{60})_2$ (where R^{60} is lower alkyl; or lower alkenyl); $-(CH_2)_oSO_2R^{62}$ (where R^{62} is lower alkyl; or lower alkenyl); or $-(CH_2)_qC_6H_4R^8$ (where R^8 is H; F; Cl; CF_3 ; lower alkyl;
 30 lower alkenyl; or lower alkoxy).
16. Compounds according to claim 15 wherein R^1 is H; R^{20} is H; R^{30} is H; R^{31} is carboxymethyl; or lower alkoxy-carbonylmethyl; R^{32} is H; R^{35} is methyl; R^{36} is methoxy; R^{37} is H and R^{38} is H.
17. Compounds according to any one of claims 1 to 16 wherein in the chain(s) of α -amino acid residues Z, Z^1 and Z^2

- If n is 8, the amino acid residues in position 1 – 8 are:
 - P1: of type C or of type D; or of type E;
 - P2: of type E; or of type D;
 - P3: of type E;
 - 5 - P4: of type E or of formula -A1-A69-CO-;
 - P5: of type E or of formula -B-CO-;
 - P6: of type D;
 - P7: of type E; or of type D and
 - P8: of type C or of type D; or of type E;
 - 10 - at P4 and P5 also D-isomers being possible;
- if n is 9, the amino acid residues in position 1 – 9 are:
 - P1: of type C or of type D; or of type E;
 - P2: of type E; or of type D;
 - P3: of type C;
 - 15 - P4: of type E, or the residue is Pro;
 - P5: of type E, or the residue is Pro;
 - P6: of type D or of type E, or the residue is Pro;
 - P7: of type E or of type D;
 - P8: of type E; or of type D and
 - 20 - P9: of type C or of type D; or of type E;
 - at P4, P5 and P6 also D-isomers being possible;
- if n is 10, the amino acid residues in position 1 – 10 are:
 - P1: of type C or of type D; or of type E;
 - P2: of type E; or of type D;
 - 25 - P3: of type C;
 - P4: of type E or of type D;
 - P5: of type E or of formula -A1-A69-CO-;
 - P6: of type E or of formula -B-CO-;
 - P7: of type D or of type E;
 - 30 - P8: of type D;
 - P9: of type E; or of type D and
 - P10: of type C or of type D; or of type E;
 - at P5 and P6 also D-isomers being possible;
- if n is 11, the amino acid residues in position 1 – 11 are:
 - 35 - P1: of type C or of type D; or of type E;
 - P2: of type E; or of type D;
 - P3: of type D;

- P4: of type E or of type C;
- P5: of type E, or the residue is Pro;
- P6: of type E, or the residue is Pro;
- P7: of type E, or the residue is Pro;
- 5 - P8: of type D or of type E;
- P9: of type D;
- P10: of type E; or of type D and
- P11: of type C or of type D; or of type E;
- at P5, P6 and P7 also D-isomers being possible;
- 10 - if n is 12, the amino acid residues in position 1 – 12 are:
 - P1: of type C or of type E; or of type D; or of type F;
 - P2: of type E; or of type D;
 - P3: of type C or of type D;
 - P4: of type E;
 - 15 - P5: of type E; or of type C;
 - P6: of type E or of type F or of formula -A1-A69-CO-;
 - P7: of type E or of formula -B-CO-;
 - P8: of type D;
 - P9: of type E or of type D;
 - 20 - P10: of type D;
 - P11: of type E; or of type D and
 - P12: of type C or of type E; or of type D; or of type F;
 - at P6 and P7 also D-isomers being possible;
 - if n is 13, the amino acid residues in position 1 – 13 are:
 - 25 - P1: of type C or of type D; or of type E;
 - P2: of type E; or of type D;
 - P3: of type C or of type D;
 - P4: of type E or of type C;
 - P5: of type E or of type D;
 - 30 - P6: of type E or of type F, or the residue is Pro;
 - P7: of type E, or the residue is Pro;
 - P8: of type D, or the residue is Pro;
 - P9: of type D;
 - P10: of type E or of type C;
 - 35 - P11: of type C or of type D;
 - P12: of type E; or of type D and
 - P13: of type C or of type D; or of type E;

- at P6, P7 and P8 also D-isomers being possible;
- if **n** is 14, the amino acid residues in position 1 – 14 are:
 - P1: of type C or of type D; or of type E;
 - P2: of type E; or of type D;
 - 5 - P3: of type C or of type D;
 - P4: of type D;
 - P5: of type E;
 - P6: of type E;
 - P7: of type E or of type F or of formula -A1-A69-CO-;
 - 10 - P8: of type E or of formula -B-CO-;
 - P9: of type D;
 - P10: of type C;
 - P11: of type E or of type D;
 - P12: of type D or of type C;
 - 15 - P13: of type E; or of type D and
 - P14: of type C or of type D; or of type E;
 - at P7 and P8 also D-isomers being possible;
- if **n** is 15, the amino acid residues in position 1 – 15 are:
 - P1: of type C and of type D; or of type E;
 - 20 - P2: of type E; or of type D;
 - P3: of type C and of type D;
 - P4: of type E or of type C;
 - P5: of type C;
 - P6: of type E or of type D;
 - 25 - P7: of type C, or the residue is Pro;
 - P8: of type E or of type F, or the residue is Pro;
 - P9: of type E or of type F, or the residue is Pro;
 - P10: of type E;
 - P11: of type C;
 - 30 - P12: of type E or of type C;
 - P13: of type D or of type C;
 - P14: of type E; or of type D and
 - P15: of type C and of type D; or of type E;
 - at P7, P8 and P9 also D-isomers being possible; and
- 35 - if **n** is 16, the amino acid residues in position 1 – 16 are:
 - P1: of type D; or of type E;
 - P2: of type E; or of type D;

- P3: of type C or of type D;
- P4: of type E or of type D;
- P5: of type D;
- P6: of type E;
- 5 - P7: of type E or of type F;
- P8: of type E or of type F or of formula -A1-A69-CO-;
- P9: of type E or of formula -B-CO-;
- P10: of type D;
- P11: of type E;
- 10 - P12: of type D;
- P13: of type E or of type C;
- P14: of type C or of type D;
- P15: of type E; or of type D and
- P16: of type C or of type D; or of type E;
- 15 - at P8 and P9 also D-isomers being possible.

18. Compounds according to claim 17 wherein n is 12 and the amino acid residues in position 1 – 12 are:

- P1: Leu; Arg; Lys; Tyr; Trp; Val; Gln; or 4-AmPhe;
- 20 - P2: Arg; Trp; or Gln;
- P3: Leu; Val; Ile; or Phe;
- P4: Lys; Arg; Gln; or Orn;
- P5: Lys; or Arg;
- P6: Arg; Y(Bzl); or ^DY(Bzl)
- 25 - P7: Arg;
- P8: Trp; Bip; 1-Nal; Y(Bzl); or Val;
- P9: Lys; Arg; Orn; Tyr; Trp; or Gln;
- P10: Tyr; T(Bzl); or Y(Bzl);
- P11: Arg; or Tyr; and
- 30 - P12: Val; Arg; 1-Nal; or 4-AmPhe.

19. A compound of formula Ia according to claim 1 wherein the template is ^DPro-^LPro; n is 12; and the amino acid residues in position 1 – 12 are:

- P1: Leu;
- 35 - P2: Arg;
- P3: Leu;
- P4: Lys;

- 5
- P5: Lys;
 - P6: Arg;
 - P7: Arg;
 - P8: Trp;
 - P9: Lys;
 - P10: Tyr;
 - P11: Arg; and
 - P12: Val.

- 10 20. A compound of formula Ia according to claim 1 wherein the template is ^DPro-^LPro; n is 12; and the amino acid residues in position 1 – 12 are:

- 15
- P1: Leu;
 - P2: Arg;
 - P3: Leu;
 - P4: Lys;
 - P5: Lys;
 - P6: Arg;
 - P7: Arg;
 - P8: Y(Bzl);
 - 20 - P9: Lys;
 - P10: Tyr;
 - P11: Arg; and
 - P12: Val.

- 25 21. A compound of formula Ia according to claim 1 wherein the template is ^DPro-^LPro; n is 12; and the amino acid residues in position 1 – 12 are:

- 30
- P1: Leu;
 - P2: Arg;
 - P3: Leu;
 - P4: Lys;
 - P5: Lys;
 - P6: Arg;
 - P7: Arg;
 - P8: Trp;
 - 35 - P9: Lys;
 - P10: Tyr;
 - P11: Arg; and

- P12: 1-Nal.

22. A compound of formula Ia according to claim 1 wherein the template is ^DPro-^LPro; n is 12; and the amino acid residues in position 1 – 12 are:

5 - P1: Leu;
 - P2: Arg;
 - P3: Leu;
 - P4: Lys;
 - P5: Lys;
10 - P6: Arg;
 - P7: Arg;
 - P8: Bip;
 - P9: Lys;
 - P10: Tyr;
15 - P11: Arg; and
 - P12: Val.

23. A compound of formula Ia according to claim 1 wherein the template is ^DPro-^LPro; n is 12; and the amino acid residues in position 1 – 12 are:

20 - P1: Leu;
 - P2: Arg;
 - P3: Leu;
 - P4: Lys;
 - P5: Lys;
25 - P6: Arg;
 - P7: Arg;
 - P8: Trp;
 - P9: Lys;
 - P10: T(Bzl);
30 - P11: Arg; and
 - P12: Val.

24. A compound of formula Ia according to claim 1 wherein the template is ^DPro-^LPro; n is 12; and the amino acid residues in position 1 – 12 are:

35 - P1: Leu;
 - P2: Arg;
 - P3: Leu;

- P4: Lys;
- P5: Lys;
- P6: Arg;
- P7: Arg;
- 5 - P8: Trp;
- P9: Arg;
- P10: Tyr;
- P11: Arg; and
- P12: Val.

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25. A compound of formula Ia according to claim 1 wherein the template is ^DPro-^LPro; n is 12; and the amino acid residues in position 1 – 12 are:

- P1: Leu;
- P2: Trp;
- 15 - P3: Leu;
- P4: Lys;
- P5: Lys;
- P6: Arg;
- P7: Arg;
- 20 - P8: Bip;
- P9: Lys;
- P10: Tyr;
- P11: Arg; and
- P12: Val.

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26. A compound of formula Ia according to claim 1 wherein the template is ^DPro-Phe; n is 12; and the amino acid residues in position 1 – 12 are:

- P1: Leu;
- P2: Arg;
- 30 - P3: Leu;
- P4: Lys;
- P5: Lys;
- P6: Arg;
- P7: Arg;
- 35 - P8: Trp;
- P9: Lys;
- P10: Tyr;

- P11: Arg; and
- P12: Val.

27. A compound of formula Ia according to claim 1 wherein the template is ^DPro-(2R,4S)-
5 4-[n-hexylcarbonylamino]-^LPro; n is 12; and the amino acid residues in position 1 – 12 are:

- P1: Leu;
- P2: Arg;
- P3: Leu;
- P4: Lys;
- 10 - P5: Lys;
- P6: Arg;
- P7: Arg;
- P8: Trp;
- P9: Lys;
- 15 - P10: Tyr;
- P11: Arg; and
- P12: Val.

28. A compound of formula Ia according to claim 1 wherein the template is ^DPro-(2R,4S)-
20 4-[cyclohexylcarbonylamino]-^LPro; n is 12; and the amino acid residues in position 1 – 12
are:

- P1: Leu;
- P2: Arg;
- P3: Leu;
- 25 - P4: Lys;
- P5: Lys;
- P6: Arg;
- P7: Arg;
- P8: Trp;
- 30 - P9: Lys;
- P10: Tyr;
- P11: Arg; and
- P12: Val.

35 29. A compound according to claim 1 wherein the template is of formula (c1) wherein R²⁰
is H; R³⁵ is methyl; R³⁶ is methoxy; R³⁷ is H and R³⁸ is H; n is 12; and the amino acid residues

in position

1 – 12 are:

- P1: Leu;
- P2: Arg;
- 5 - P3: Leu;
- P4: Lys;
- P5: Lys;
- P6: Arg;
- P7: Arg;
- 10 - P8: Trp;
- P9: Lys;
- P10: Tyr;
- P11: Arg; and
- P12: Val.

15

30. A compound of formula Ia according to claim 1 wherein the template is ^DPro-^LPro; n is 12; and the amino acid residues in position 1 – 12 are:

- P1: Arg;
- P2: Trp;
- 20 - P3: Leu;
- P4: Lys;
- P5: Lys;
- P6: Arg;
- P7: Arg;
- 25 - P8: Trp;
- P9: Lys;
- P10: Tyr;
- P11: Tyr; and
- P12: Val.

30

31. A compound of formula Ia according to claim 1 wherein the template is ^DPro-^LPro; n is 12; and the amino acid residues in position 1 – 12 are:

- P1: Leu;
- P2: Trp;
- 35 - P3: Leu;
- P4: Lys;
- P5: Lys;

- P6: Arg;
- P7: Arg;
- P8: Trp;
- P9: Lys;
- 5 - P10: Tyr;
- P11: Tyr; and
- P12: Arg.

32. A compound of formula Ia according to claim 1 wherein the template is ^DPro-^LPro; n is
10 12; and the amino acid residues in position 1 – 12 are:

- P1: Arg;
- P2: Trp;
- P3: Leu;
- P4: Lys;
- 15 - P5: Lys;
- P6: Arg;
- P7: Arg;
- P8: Trp;
- P9: Lys;
- 20 - P10: Tyr;
- P11: Tyr; and
- P12: Arg.

33. A compound of formula Ia according to claim 1 wherein the template is ^DPro-^LPro; n is
25 12; and the amino acid residues in position 1 – 12 are:

- P1: Leu;
- P2: Arg;
- P3: Leu;
- P4: Lys;
- 30 - P5: Lys;
- P6: ^DY(Bzl);
- P7: Arg;
- P8: Trp;
- P9: Lys;
- 35 - P10: Tyr;
- P11: Arg; and
- P12: Val.

34. A compound of formula Ia according to claim 1 wherein the template is ^DPro-^LPro; n is 12; and the amino acid residues in position 1 – 12 are:

- P1: Arg;
- 5 - P2: Bip;
- P3: Leu;
- P4: Lys;
- P5: Lys;
- P6: Arg;
- 10 - P7: Arg;
- P8: Trp;
- P9: Lys;
- P10: Tyr;
- P11: Tyr; and
- 15 - P12: Arg.

35. A compound of formula Ia according to claim 1 wherein the template is ^DPro-^LPro; n is 12; and the amino acid residues in position 1 – 12 are:

- P1: Lys;
- 20 - P2: Trp;
- P3: Leu;
- P4: Lys;
- P5: Lys;
- P6: Arg;
- 25 - P7: Arg;
- P8: Trp;
- P9: Lys;
- P10: Tyr;
- P11: Tyr; and
- 30 - P12: Arg.

36. A compound of formula Ia according to claim 1 wherein the template is ^DPro-^LPro; n is 12; and the amino acid residues in position 1 – 12 are:

- P1: Tyr;
- 35 - P2: Trp;
- P3: Leu;
- P4: Lys;

- P5: Lys;
- P6: Arg;
- P7: Arg;
- P8: Trp;
- 5 - P9: Lys;
- P10: Tyr;
- P11: Tyr; and
- P12: Arg.

10 37. A compound of formula Ia according to claim 1 wherein the template is ^DPro-^LPro; n is 12; and the amino acid residues in position 1 – 12 are:

- P1: Trp;
- P2: Trp;
- P3: Leu;
- 15 - P4: Lys;
- P5: Lys;
- P6: Arg;
- P7: Arg;
- P8: Trp;
- 20 - P9: Lys;
- P10: Tyr;
- P11: Tyr; and
- P12: Arg.

25 38. A compound of formula Ia according to claim 1 wherein the template is ^DPro-^LPro; n is 12; and the amino acid residues in position 1 – 12 are:

- P1: Val;
- P2: Trp;
- P3: Leu;
- 30 - P4: Lys;
- P5: Lys;
- P6: Arg;
- P7: Arg;
- P8: Trp;
- 35 - P9: Lys;
- P10: Tyr;
- P11: Tyr; and

- P12: Arg.

39. A compound of formula Ia according to claim 1 wherein the template is ^DPro-^LPro; n is 12; and the amino acid residues in position 1 – 12 are:

- 5 - P1: Gln;
 - P2: Trp;
 - P3: Leu;
 - P4: Lys;
 - P5: Lys;
10 - P6: Arg;
 - P7: Arg;
 - P8: Trp;
 - P9: Lys;
 - P10: Tyr;
15 - P11: Tyr; and
 - P12: Arg.

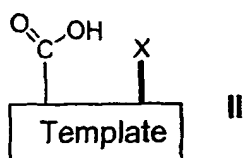
40. A compound of formula Ia according to claim 1 wherein the template is ^DPro-^LPro; n is 12; and the amino acid residues in position 1 – 12 are:

- 20 - P1: Leu;
 - P2: Arg;
 - P3: Leu;
 - P4: Lys;
 - P5: Lys;
25 - P6: Y(Bzl);
 - P7: Arg;
 - P8: Trp;
 - P9: Lys;
 - P10: Tyr;
30 - P11: Arg; and
 - P12: Val.

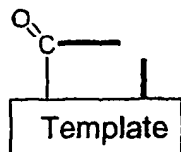
41. Enantiomers of the compounds of formulae Ia and Ib as defined in claim 1.

42. Compounds according to any one of claims 1 to 41 for use as therapeutically active
35 substances.

43. A pharmaceutical composition containing a compound according to any one of claims 1 to 41 and a pharmaceutically inert carrier.
44. Compositions according to claim 43 in a form suitable for oral, topical, transdermal, injection, buccal, transmucosal, pulmonary or inhalation administration.
45. Compositions according to claim 43 or 44 in form of tablets, dragees, capsules, solutions, liquids, gels, plasters, creams, ointments, syrups, slurries, suspensions, sprays, nebulisers or suppositories.
46. The use of compounds according to any one of claims 1 to 41 for the manufacture of a medicament for treating or preventing infections or diseases related to such infections, said infections being in particular cystic fibrosis lung infections, or for the manufacture of a medicament useful against malignant cells for treatment of cancer.
47. The use of compounds according to any one of claims 1 to 41 as disinfectants or preservatives for foodstuffs, cosmetics, medicaments and other nutrient-containing materials.
48. The use of compounds according to claims 1-41 for preventing surfaces from microbial colonisation.
49. A process for the manufacture of compounds according to any one of claims 1 to 40 which process comprises
- (a) coupling an appropriately functionalized solid support with an appropriately N-protected derivative of that amino acid which in the desired end-product is in position $n/2$, $n/2+1$ or $n/2-1$ if n is an even number and, respectively, in position $n/2+1/2$ or $n/2-1/2$ if n is an odd number, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;
- (b) removing the N-protecting group from the product thus obtained;
- (c) coupling the product thus obtained with an appropriately N-protected derivative of that amino acid which in the desired end-product is one position nearer the N-terminal amino acid residue, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;
- (d) removing the N-protecting group from the product thus obtained;
- (e) repeating, if necessary, steps (c) and (d) until the N-terminal amino acid residue has been introduced;
- (f) coupling the product thus obtained to a compound of the general formula

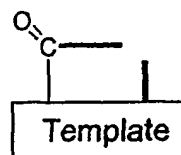


wherein



is as defined above and X is an N-protecting group or, if

5



is to be group (a1) or (a2), above, alternatively

(fa) coupling the product obtained in step (d) or (e) with an appropriately N-protected derivative of an amino acid of the general formula

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wherein B and A are as defined above, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

(fb) removing the N-protecting group from the product thus obtained; and

(fc) coupling the product thus obtained with an appropriately N-protected derivative of an amino acid of the above general formula IV and, respectively, III, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

15

(g) removing the N-protecting group from the product obtained in step (f) or (fc);

(h) coupling the product thus obtained to an appropriately N-protected derivative of that

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amino acid which in the desired end-product is in position n, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

(i) removing the N-protecting group from the product thus obtained;

(j) coupling the product thus obtained to an appropriately N-protected derivative of that amino acid which in the desired end-product is one position farther away from position n, any

25

functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

(k) removing the N-protecting group from the product thus obtained;

(l) repeating, if necessary, steps (j) and (k) until all amino acid residues have been introduced;

- (m) if desired, selectively deprotecting one or several protected functional group(s) present in the molecule and appropriately substituting the reactive group(s) thus liberated;
- (o) detaching the product thus obtained from the solid support;
- (p) cyclizing the product cleaved from the solid support;
- 5 (q) if, desired
 - (qa) forming one or several interstrand linkage(s) between side-chains of appropriate amino acid residues at opposite positions of the β -strand region; and/or
 - (qb) connecting two building blocks of the type of formula Ia via a bridge
-G1 - L - G2-;
- 10 (r) removing any protecting groups present on functional groups of any members of the chain of amino acid residues and, if desired, any protecting group(s) which may in addition be present in the molecule; and
- (s) if desired, converting the product thus obtained into a pharmaceutically acceptable salt or converting a pharmaceutically acceptable, or unacceptable, salt thus obtained into the
- 15 corresponding free compound of formula I or into a different, pharmaceutically acceptable, salt.

50. A modification of the process of claim 49 for the manufacture of compounds according to claim 41 in which enantiomers of all chiral starting materials are used.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/01711

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K7/06 C07K7/08 C07K1/04 A61K38/08 A61K38/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, MEDLINE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FAVRE ET AL: "STRUCTURAL MIMICRY OF CANONICAL CONFORMATIONS IN ANTIBODY HYPERVARIABLE LOOPS USING CYCLIC PEPTIDES CONTAINING A HETEROCHIRAL DIPROLINE TEMPLATE" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, XX, XX, vol. 121, no. 12, 31 March 1999 (1999-03-31), pages 2679-2685, XP002137023 ISSN: 0002-7863 the whole document	1-42
A	US 5 916 872 A (CHANG CONWAY ET AL) 29 June 1999 (1999-06-29) cited in the application the whole document	1-49
-/-		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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A document member of the same patent family

Date of the actual completion of the international search

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Date of mailing of the international search report

09/07/2002

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/01711

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	OBRECHT D ET AL: "NOVEL PEPTIDE MIMETIC BUILDING BLOCKS AND STRATEGIES FOR EFFICIENT LEAD FINDING" ADVANCES IN MEDICINAL CHEMISTRY, JAI PRESS,, US, April 1999 (1999-04), pages 1-68, XP002137026 page 28, last paragraph -page 43	1-50
A	JOHN A. ROBINSON: "The Design, Synthesis and Conformation of Some New beta-Hairpin Mimetics: Novel Reagents for Drug and Vaccine Discovery" SYNLETT, vol. 1999, no. 4, April 2000 (2000-04), pages 429-441, XP001080054 Stuttgart, DE paragraphs '0003!, '0004!	1-50
A	LUJONG JIANG, KERSTIN MOEHLE, BOOPATHY DHANAPAL, DANIEL OBRECHT, JOHN A. ROBINSON : "Combinatorial Biomimetic Chemistry: Parallel Synthesis of a Small Library of beta-Hairpin Mimetics Based on Loop III from Human Platelet-Derived Growth Factor B" HELVETICA CHIMICA ACTA, vol. 83, no. 12, December 2000 (2000-12), pages 3097-3112, XP002202283 Zürich, CH the whole document	1-42, 50
A	MCINNES CAMPBELL ET AL: "Development of the structural basis for antimicrobial and hemolytic activities of peptides based on gramicidin S and design of novel analogs using NMR spectroscopy." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 275, no. 19, 12 May 2000 (2000-05-12), pages 14287-14294, XP002202322 ISSN: 0021-9258 cited in the application the whole document	1, 43-49

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/01711

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-42 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed, i.e. for peptides fixed with a D-Pro-L-Pro template. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the peptides fixed with a D-Pro-L-Pro as disclosed in the examples.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/01711

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5916872	A	29-06-1999	AU 720100 B2	25-05-2000
			AU 3963097 A	10-02-1998
			CA 2261797 A1	29-01-1998
			EP 0956029 A1	17-11-1999
			JP 2001503020 T	06-03-2001
			WO 9803192 A1	29-01-1998

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
12 September 2002 (12.09.2002)

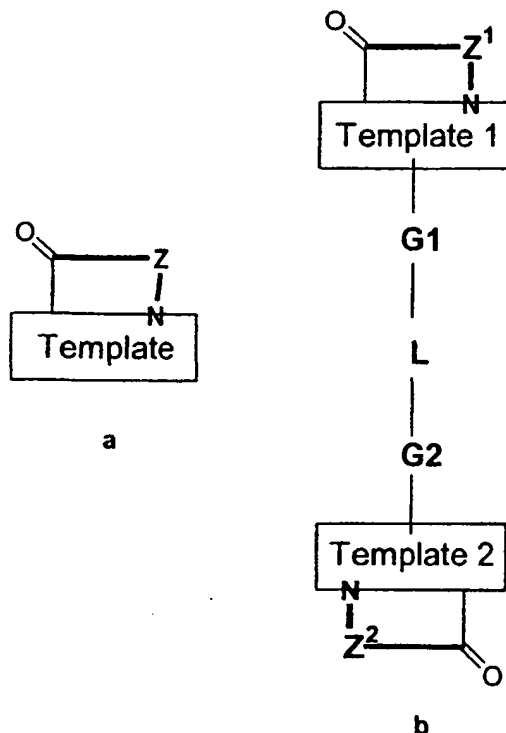
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(10) International Publication Number
WO 02/070547 A1

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- (21) International Application Number: PCT/EP02/01711
- (22) International Filing Date: 18 February 2002 (18.02.2002)
- (25) Filing Language: English
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- (71) Applicants (for all designated States except US):
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- (75) Inventors/Applicants (for US only): OBRECHT, Daniel [CH/CH]; Seltisbergerstrasse 30, CH-4059 Basel (CH). ROBINSON, John, Anthony [GB/CH]; Tobelstrasse 24, CH-8615 Wermatswil (CH). VRIJBLOED, Jan, Wim [NL/CH]; Vorhaldenstrasse 14, CH-8049 Zürich (CH).
- (74) Agent: BRAUN, André; Braun & Partner, Reussstrasse 22, CH-4054 Basel (CH).
- (81) Designated States (*national*): AE, AG, AL, AM, AT (utility model), AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, ES, FI (utility model), FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK (utility model), SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:
— with international search report

[Continued on next page]

(54) Title: TEMPLATE-FIXED PEPTIDOMIMETICS WITH ANTIMICROBIAL ACTIVITY



(57) Abstract: Template-fixed β -hairpin peptidomimetics of the general formulae (I) and (II) wherein Z, Z1 and Z2 are template-fixed chains of 8 to 16 α -amino acid residues which, depending on their positions in the chain (counted starting from the N-terminal amino acid) are Gly, or Pro, or of certain types which, as the remaining symbols in the above formulae, are defined in the description and the claims, and salts thereof, have the property to inhibit the growth of or to kill microorganisms and cancer cells. They can be used as disinfectants for foodstuffs, cosmetics, medicaments or other nutrient-containing materials or as medicaments to treat or prevent infections or diseases related to such infections and/or cancer. These β -hairpin peptidomimetics can be manufactured by a process which is based on a mixed solid- and solution phase synthetic strategy.

WO 02/070547 A1

- (48) Date of publication of this corrected version:
30 October 2003
- (15) Information about Correction:
see PCT Gazette No. 44/2003 of 30 October 2003, Section II

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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